Sponsor: Sanofi **Drug substance(s):** SAR443216	**Study Identifiers:** IND: 147924 EudraCT Number: 2021-000086-32 NCT: NCT05013554 WHO: U1111-1253-2233 **Study code:** TED16925

Title of the study:

A Phase 1/1b Open-label, First-in-human, Single Agent, Dose Escalation and Expansion Study for the Evaluation of Safety, Pharmacokinetics, Pharmacodynamics, and Anti-tumor Activity of SAR443216 in Participants With Relapsed/Refractory HER2 Expressing Solid Tumors

Study center(s):

This study was conducted at 10 centers that enrolled participants in the United States, France, Spain, Taiwan, and the Republic of Korea.

Study period:

Study initiation date (first subject first visit): 16 August 2021

Study end date (last subject last visit): 15 January 2024

Study Status: Terminated (Sponsor's decision. Termination decision unrelated to safety profile)

Phase of development: Phase 1/1b

Objectives:

Primary

Part 1 (Dose Escalation)

- To determine the maximum tolerated dose/maximum administered dose of SAR443216 administered as a single agent in participants with HER2 expressing solid tumors and determine the recommended doses for IV and SC administration in the dose escalation part.
- To determine the safety of SAR443216 after IV and SC administration.

Part 2 (Dose Expansion)

- To assess preliminary clinical activity of single agent SAR443216 after IV and SC administration at the recommended doses in participants with HER2 expressing solid tumors, with various levels of HER2 expression.

Secondary

(Part 1)

- To assess preliminary clinical activity of single agent SAR443216 after IV and SC administration at the recommended doses in participants with HER2 expressing solid tumors, with various levels of HER2 expression

(Part 2)

- To determine the safety of SAR443216.

(Part 1 and Part 2)

- To characterize the pharmacokinetic (PK) profile of SAR443216 when administered as a single agent after IV and SC (Part 1 only) administration.
- To evaluate the potential immunogenicity of SAR443216 after IV and SC administration.
- To assess preliminary clinical activity of single agent SAR443216 at the recommended doses in participants with HER2 expressing solid tumors, with various levels of HER2 expression

Methodology:

This was a Phase 1/1b open-label, first-in-human, multicenter, non-randomized, single agent study to evaluate the safety, pharmacokinetics, pharmacodynamics, and signs of clinical activity of SAR443216 administered intravenously or subcutaneously in participants with solid tumors.

To minimize the risk of severe Cytokine Release Syndrome (CRS), an intra-participant dose escalation (lead-in doses) was used in Cycle 1. For the IV cohort, a 2-week (IV cohort) and an extended 3-week lead-in period (IV-ext cohort) were tested.

The study was intended to include 2 parts:

・A dose escalation part for safety and dose finding: To be conducted in participants with advanced relapsed or refractory solid tumors that express HER2 as defined by an in situ validated HER2 diagnostic test or with detected HER2 genomic aberrations in tissue or blood using a validated test, and who have exhausted all standard of care therapy.

・A dose expansion part for the assessment of safety and preliminary clinical activity: To be conducted at recommended doses in various cohorts defined by HER2 expression and/or HER2 genomic aberrations.

Number of study participants:

- A maximum of approximately 54 DLT-evaluable participants were planned for the IV dose escalation part and approximately 16 DLT-evaluable participants were planned for inclusion in the SC dose escalation part. There was no formal sample size calculation. Participants were planned to be included in cohorts of 4 (or more) to ensure at least 3 participants were evaluable for DLT during the DLT observation period.
- For the dose expansion part, 4 cohorts were planned, with approximately 40, 30, 30, and 30 (total 130) participants for Cohort A, B, C, and D respectively.
  - Cohort A: Participants with metastatic breast cancers with HER2 IHC 3+ or 2+ (with HER2 amplification)
  - Cohort B: Participants with metastatic breast cancers with HER2 IHC 1+ or 2+ (without HER2 amplification) or HER2 activating mutation
  - Cohort C: Participants with metastatic gastric cancers with HER2 IHC 1+ or 2+ (without HER2 amplification) or HER2 activating mutation
  - Cohort D: Participants with metastatic NSCLC with HER2 IHC 1+, 2+, 3+, and/or HER2 amplification and/or HER2 activating mutation
- It was anticipated that a maximum of approximately 200 evaluable participants would be enrolled in this study for the dose escalation and expansion parts combined.

In the dose escalation part of the study:

- Twenty-nine participants were enrolled and treated intravenously with a 2-week lead-in period. None were enrolled but not treated. There were 25 DLT-evaluable participants.
  - SAR443216 18 µg IV: 4 participants
  - SAR443216 60 µg IV: 3 participants
  - SAR443216 180 µg IV: 9 participants
  - SAR443216 240 µg IV: 4 participants
  - SAR443216 360 µg IV: 6 participants
  - SAR443216 720 µg IV: 3 participants
- Twelve participants were enrolled, and 11 were treated intravenously with an extended 3 week lead-in period. There were 8 DLT-evaluable participants.
  - SAR443216 480 µg IV: 4 participants were enrolled and treated.
  - SAR443216 720 µg IV: 4 participants were enrolled and treated.
  - SAR443216 900 µg IV: 4 participants were enrolled, with 3 participants receiving study intervention. 1 participant did not complete the study period and discontinued from the study prior to receiving study intervention due to meeting exclusion criteria after enrollment.
- Three participants were enrolled and treated subcutaneously with a 2-week lead-in period. None were enrolled but not treated. There was 1 DLT-evaluable participant.
  - SAR443216 240 µg SC: 3 participants

During the study conduct, the IV-ext cohort was implemented to mitigate the incidence and severity of cytokine release syndrome and the associated asymptomatic transaminase elevations. The enrollment to the subcutaneous administration cohort was stopped following the first 3 patients in the lowest dose-group, due to the occurrence of more severe injection site reactions

associated with CRS (all ⩽ grade 2) than expected, the confirmed relatively low bioavailability (30%), and the high predicted efficacious dose-level.

The study was stopped for reasons other than safety or efficacy before the planned enrollment was completed, and prior to identification of the maximum tolerated dose; therefore, no formal conclusions regarding efficacy are drawn. The dose expansion part of the study was not initiated.

Diagnosis and criteria for inclusion:

Adult male or female participants were eligible for this study if they had a histologically or cytologically confirmed diagnosis of metastatic solid tumors, had exhausted all locally available and clinically appropriate standard of care therapies, and had HER2 expression detected in tumor tissue or blood. Body weight was required to be within 45 and 150 kg (inclusive).

Study products

SAR443216 4.5 mg

•Formulation: SAR443216 is supplied as a sterile lyophilized powder, for solution for infusion, supplied in a single-use clear glass vial (10 mL Type I)

•Route of administration: IV infusion

•Dose regimen: Administered on D1 and D4 of the first week, then administered weekly until end of treatment.

•For IV administration, the powder was reconstituted with water for injection to 1mg/mL.

SAR443216 225µg

•Formulation: SAR443216 is supplied as a sterile lyophilized powder, for solution for infusion, supplied in a single-use clear glass vial (10 mL Type I)

•Route of administration: IV infusion

•Dose regimen: Administered on D1 and D4 of the first week, then administered weekly until end of treatment.

•For IV administration, the powder was reconstituted with water for injection to 0.05 mg/mL.

Duration of study intervention:

Escalation part: Cycle 1 Week 1, administration at D1 and D4, then weekly administration. After Cycle 1, weekly administration until the end of treatment.

Criteria for evaluation:

Primary

Part 1 (Dose Escalation)

· Incidence of dose limiting toxicities during the dose-limiting toxicity (DLT) observation period.

· Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and lab abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Part 2 (Dose Expansion)

· Objective response rate (ORR) and duration of response (DoR) of SAR443216 in all participants. ORR of SAR443216 treatment will be based on RECIST v1.1

Secondary

(Part 1)

- ORR and DoR of SAR443216 in all participants. ORR of SAR443216 treatment will be based on RECIST v1.1.

(Part 2)

- Incidence of TEAEs, SAEs, and lab abnormalities according to NCI CTCAE Version 5.0.

(Part 1 and Part 2)

- Plasma concentrations and PK parameters (C_{max}, C_{trough}, $t_{1/2}$, AUC_{0-T}) of SAR443216
- Incidence of antidrug antibodies (ADAs) against SAR443216
- Progression free survival (PFS) of SAR443216 in all participants based on RECIST v1.1

Statistical methods:

Efficacy:

Confirmed objective response based on RECIST v1.1 was defined as the proportion of participants who achieved a confirmed complete response (CR) or partial response (PR) as best overall response (BOR). The number and percentage of subjects was summarized by BOR and for objective response.

Safety:

All safety analyses were performed on the Safety Population, except DLT analyses that were performed on the DLT-evaluable population. Analyses were described in the statistical analysis plan finalized before database lock. As the study was terminated during the dose escalation part of the study, only limited analyses required to present safety and secondary endpoint data were produced.

Statistical analysis methods used for safety endpoints in the dose escalation part:

•DLTs: DLTs observed during the DLT observation period (ie, 1 week after two consecutive target doses administered) were summarized by dose level and the event occurrence with worst grade was listed. DLTs were graded using NCI CTCAE Version 5.0.

•AEs: Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the NCI CTCAE Version 5.0. For participants with multiple occurrences of the same preferred term (PT), the maximum grade was used. The number and percentage of participants experiencing TEAEs by primary SOC and PT was summarized by NCI CTCAE grade (all grades and Grade $\geqslant$3). Similar tables were prepared for treatment-related TEAEs, TE SAEs, treatment-related TE SAEs, AESIs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification and TEAEs with fatal outcome in context other than disease progression. The number and percentage of participants who died by study period and cause of death was also provided.

•Clinical laboratory evaluations: Clinical laboratory results were graded according to NCI CTCAE Version 5.0, when applicable. Shift tables displaying the number and percentage of participants by grade status (worst grade by participant in the treatment-emergent period) were provided.

Pharmacokinetics and Immunogenicity:

•Pharmacokinetics: SAR443216 was measured in plasma samples by a ligand-binding assay. Noncompartmental analysis was performed to derive PK parameters.

•Immunogenicity: Immunogenicity analyses were performed on the ADA-evaluable population. ADA incidence and kinetics of antidrug antibody responses were summarized.

Summary Results:

Demographic and other baseline characteristics:

A total of 29 participants were enrolled and treated in the initial intravenous administration (2 week lead-in) group, a total of 3 participants were enrolled and treated in the initial subcutaneous administration (2-week lead-in) group, and a total of 12 participants were enrolled, and 11 treated, in the IV-ext (3-week lead-in) group. One participant in the IV administration, 3 week lead-in group (in the 900 µg cohort) did not receive treatment due to meeting exclusion criteria after enrollment.

Most enrolled and treated participants were White, with 17 (58.6%) participants in the IV administration (2-week lead-in) group, 5 (45.5%) participants in the IV-ext (3-week lead-in) group, and 2 (66.7%) participants in the SC administration (2-week lead-in) group, or Asian, with 10 (34.5%) participants in the IV administration (2-week lead-in) group, 6 (54.5%) participants in the IV-ext (3-week lead-in) group, and 1 (33.3%) participant in the SC administration (2-week lead-in) group.

All participants were above 18 years of age. The mean (standard deviation [SD]) age was 54.6 (12.7) for the IV administration (2-week lead-in) group, 59.2 (9.3) for the IV-ext (3-week lead-in) group, and 60.7 (10.0) for the SC administration (2-week lead-in) group. The mean (standard deviation [SD]) weight (kg) was 67.71 (16.79) for the IV administration (2-week lead in) group, 68.40 (18.70) for the IV-ext (3-week lead-in) group, and 67.40 (18.99) for the SC administration (2-week lead-in) group.

Exposure:

A total of 43 participants were exposed to SAR443216 in the study. A total of 40 participants were exposed to SAR443216 IV (29 and 11 with 2-week and 3-week lead-in, respectively), and 3 participants were exposed to SAR443216 SC. The mean duration of IMP exposure was 12.3 weeks in the initial IV (2 weeks lead-in) cohort, 9.4 weeks in the IV-ext cohort, and 6.7 weeks in the SC cohort.

Safety results:

Out of 29 participants in the initial IV group, 3 (10.3%) deaths were reported during the treatment-emergent period, but none were reported as fatal TEAE in context other than disease progression, and 4 (13.8%) were reported in the post-treatment period in the IV administration (2 week lead-in) group. No deaths were reported in the IV-ext (3-week lead-in) or SC administration (2-week lead-in) groups. Overall, most participants who received SAR443216 reported at least 1 TEAE (28 [96.6%] participants [IV, 2-week lead-in], 11 [100%] participants [IV-ext, 3-week lead-in], and 3 [100%] participants [SC, 2-week lead-in]). One participant each discontinued from the IV administration (2-week lead-in) and SC administration (2-week lead-in) groups respectively due to a TEAE. No participants discontinued from IV-ext (3-week lead-in) due to a TEAE.

<u>IV Administration (2-week lead-in)</u>

Of the 7 (24.1%) deaths that occurred during the treatment-emergent or post-treatment periods in the IV administration (2-week lead-in) group, 3 (75.0%) were in the 18 µg dosing group, 2 (22.2%) were in the 180 µg dosing group, and 1 (33.3% and 25.0%, respectively) each were from the 60 µg and 240 µg dosing groups. Three (10.3%) occurred during the treatment-emergent period, all of which were associated with disease progression, while 4 (13.8%) occurred post treatment. Two (6.9%) were associated with disease progression and 2 (6.9%) with “other”. One death that was associated with “other” causes was due to metastatic colon cancer, while the second was due to unknown reasons.

One (3.4%) treatment-emergent serious AE (SAE) each of pneumonia, bone cancer, hypokalemia, radiculopathy, cardiac failure, embolism, chylothorax, pleural effusion, cholestatic jaundice, pain in extremity, asthenia, fatigue, aspartate transaminase (AST) increase, and increase in transaminases were reported. Two (6.9%) treatment-emergent SAE each of cytokine release syndrome (both related), dyspnea, and alanine transaminase (ALT) increase (both related) were reported. Three (10.3%) treatment-emergent SAE of disease progression were reported.

Six (20.7%) participants experienced treatment-emergent SAEs related to SAR443216, with 2 (6.9%) SAEs each of cytokine release syndrome and ALT increase, and 1 (3.4%) each of cardiac failure and AST increase.

Of the 28 (96.6%) of participants that experienced at least 1 TEAE, 3 each were from the 18 µg, 60 µg, and 720 µg dosing groups, 9 were from the 180 µg dosing group, 4 were from the 240 µg dosing group, and 6 were from the 360 µg dosing group. The most common TEAEs for all cohorts were cytokine release syndrome (11 [37.9%] participants), ALT increase (10 [34.5%]), pyrexia (9 [31.0%]), and AST increase (8 [27.6%]).

Twenty-four (82.8%) participants experienced at least 1 TEAE that was determined to be related to SAR443216. Of these, the most common for all cohorts were cytokine release syndrome (11 [37.9%]), ALT increase (8 [27.6%]), pyrexia (8 [27.6%]), infusion related reaction (7 [24.1%]), AST increase (7 [24.1%]), chills (4 [13.8%]), headache (4 [13.8%]), as well as myalgia, asthenia, fatigue, and nausea, with 3 (10.3%) events each.

Fifteen (51.7%) participants experienced Grade ⩾3 TEAEs. Five (17.2%) experienced ALT increase, 4 (13.8%) experienced AST increase, and 3 (10.3%) experienced disease progression. One (3.4%) participant experienced each of anemia, fatigue, asthenia, back pain, pneumonia, pain in extremities, cholestatic jaundice, international normalized ratio (INR) increase, pleural effusion, pulmonary embolism, transaminase increase, and wound hemorrhage.

Seven (24.1%) participants experienced Grade ⩾3 TEAEs that were determined to be related to SAR443216. These TEAEs were ALT increase (5 [17.2%]), AST increase (4 [13.8%]), and transaminase increase (1 [3.4%]).

Nine (31.0%) participants across all cohorts reported adverse events of special interest (AESIs), none of which were deemed Grade ⩾3 TEAEs. One each was from the 18 µg and 360 µg groups, 2 were from the 180 µg and 240 µg groups, and 3 were from the 720 µg group. Five (17.2%) participants developed cytokine release syndrome, 1 (3.4%) experienced cardiac failure, and 4 (13.8%) experienced infusion related reaction.

Three DLTs were reported in the IV (2-week lead-in) group: 1 in the 180 µg dose group (a Grade 2 cardiac failure), and 2 in the 720 µg dose group (both maximum Grade 4 ALT elevation).

IV Extended Administration (3-week lead-in)

In the IV-ext (3-week lead-in) group, 1 treatment-emergent serious AE (SAE) each of urinary tract infection, lung opacity, and biliary obstruction were reported. None were reported as related to treatment.

All 11 (100%) participants experienced at least 1 TEAE, and 3 (27.3%) experienced a Grade ≥3 TEAE. Of the Grade ≥3 TEAEs, 1 each came from the 480 µg, 720 µg, and 900 µg groups. The Grade ≥3 TEAEs were ALT increase, AST increase, and biliary obstruction, with 1 (9.1%) participant for each. One (9.1%) participant with Grade ≥3 TEAE of ALT and AST increase was determined to be related to treatment.

Of the TEAEs of all grades, the most common were cytokine release syndrome with 9 (81.8%) participants, pyrexia (5 [45.5%]), and infusion site reactions (4 [36.4%]). All 11 (100%) participants' experienced at least 1 TEAEs of all grades which was determined to be related to SAR443216.

Three (27.3%) participants across all cohorts reported AESI, none of which were deemed Grade ≥3 TEAEs. Two were from the 480 µg group, and 1 was from the 720 µg group. One (9.1%) participant reported cytokine release syndrome, and 3 (27.3%) reported infusion site reactions.

No DLTs were reported in the IV (3-week lead-in) group.

SC Administration (2-week lead-in)

In the SC administration (2-week lead-in) group, 1 treatment-emergent serious AE (SAE) each of cytokine release syndrome, pleural effusion, fatigue, and injection site reaction were reported. Two (66.7%) participants were determined to have experienced SAE related to SAR443216, with cytokine release syndrome (1 [33.3%]) and injection site reaction (1 [33.3%]).

All 3 (100%) participants experienced at least 1 TEAE, of which none were Grade ⩾3 TEAEs. All 3 (100%) experienced injection site reaction, and 2 (66.7%) experienced cytokine release syndrome. The following TEAEs were each experienced by 1 (33.3%) participant: ALT increase, AST increase, asthenia, fatigue, abnormal hepatic function, influenza, nausea, neutrophil count increase, pleural effusion, pyrexia, soft tissue inflammation, weight increase, and WBC increase. All 3 (100%) participants were determined to have experienced at least one TEAE related to SAR443216, including all instances of cytokine release syndrome and injection site reaction.

No participants were reported to experience any DLTs or AESIs.

Pharmacokinetics and Immunogenicity results:

Preliminary pharmacokinetic (PK) analysis was performed with PK data obtained from the IV dosed participants of the 2-week lead in phase. After IV dosing, SAR443216 showed pharmacokinetic characteristics roughly dose-proportional in the explored dose range (18 to 720 µg). Mean maximum SAR443216 concentrations increased from 1.9 ng/mL for the 18 µg dose to 96 ng/mL for the 720 µg dose. The exposures were characterized by a moderate to high variability, with CV% from 30% to >100%. The individual terminal half-lives (t1/2) were generally between 20 to 50 hours.

The initial results obtained from the 3 participants in the SC administration cohort confirmed a low SC bioavailability with plasma concentrations generally 3 times lower than observed after IV dosing with the same dose.

Treatment-emergent ADA was confirmed for 8 (27.6%) out of 29 participants in the initial IV cohort, for 1 (9.1%) out of 11 participants in the IV-ext cohort, and for 1 (33.3%) out of 3 participants in the SC cohort.

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