Sponsor: Sanofi **Drug substance(s):** SAR444245 (THOR-707)	**Study Identifiers:** IND: 156423 EudraCT/EU trial number: 2021-002105-99 NCT: NCT05061420 WHO: U1111-1251-5073 **Study code:** ACT16903

Title of the study:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with head and neck squamous cell carcinoma (HNSCC)

Study center(s):

This study was conducted at 27 centers that enrolled participants in 12 countries (USA, Canada, Argentina, Chile, France, Germany, Italy, Netherlands, Spain, South Korea, and Taiwan).

Study period:

Study initiation date: 08 October 2021 (signed informed consent)

Study completion date: 26 November 2024

Study Status: Terminated. (Early discontinuation based on strategic sponsor decision not driven by any safety concerns.)

Phase of development: Phase 2

Objectives:

Primary

- Objective response rate (ORR) defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary

- Incidence of TEAEs, SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading
- Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1
- Duration of Response (DOR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first

- Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1)
- Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of first documented disease progression determined by Investigator as per RECIST 1.1, or death due to any cause, whichever occurs first
- Plasma concentrations of SAR444245
- Incidence of anti-drug antibodies (ADAs) against SAR444245

Methodology:

This was a Phase 2, multi-cohort, uncontrolled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245-based therapies in participants with HNSCC.

Four cohorts assessing SAR444245 in combination with pembrolizumab or cetuximab with or without chemotherapy were initially planned. An overview of the study intervention to be administered and disease indication being treated for each cohort is provided in Table 1.

Table 1 - Overview of study cohorts

Cohort	Study intervention	Disease
A1	SAR444245 + pembrolizumab	R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1
A2	SAR444245 + cetuximab + pembrolizumab	R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1
B1	SAR444245 + pembrolizumab	R/M HNSCC treated with PD1/PD-L1-based regimen & platinum-based regimen after failure of no more than 2 regimens for R/M disease
B2	SAR444245 + cetuximab	R/M HNSCC treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease

CPS: combined positive score; HNSCC: Head and neck squamous cell carcinoma; PD1: Programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; R/M: Recurrent/metastatic.

The study was to consist of a core phase for all 4 cohorts, with a safety run-in (planned for Cohort A2) and an expansion phase for specific cohorts (Cohorts B1 and B2).

On 25 May 2022, the Investigators were informed by memo that Cohort A2 would not be initiated in order to concentrate Phase 2 development efforts on the therapeutic potential of SAR444245 in the already selected combination regimens.

The Sponsor decided to terminate the study early for non-safety reasons on 21 October 2022. Following preliminary assessments performed across all SAR444245 studies in the Phase 1/2 program, observed antitumor activity at the current dose and schedule of Q3W in combination with pembrolizumab or cetuximab was lower than projected. The safety profile of SAR444245 in combination with pembrolizumab or cetuximab was manageable, with no actions needed for safety reasons.

Number of study participants:

Approximately 40 participants were to be enrolled and were to receive the confirmed safe dose per cohort. Of the 4 treatment cohorts planned in the study, 3 were initiated prior to the Sponsor's decision to terminate the study.

The actual number of participants analyzed per analysis population is shown for Cohorts A1 in Table 2 and for Cohorts B1 and B2 in Table 3.

Table 2 - Analysis populations - Cohort A1

n (%)	Cohort A1 SAR444245 24 ug/kg + pembro (N=20)
Enrolled population	20
Exposed population	20 (100)
Population without trial impact (disruption) due to COVID-19	20 (100)
Efficacy population	20 (100)
PDy population	20 (100)

Percentages are calculated using the number of participants exposed as denominator

Extraction date: 11OCT2023

PGM=PRODOPS/SAR444245/ACT16903/CSR/REPORT/PGM/dis_ana_pop_a_t.sas
OUT=REPORT/OUTPUT/dis_ana_pop_a1_a_t_i.rtf (06FEB2024 7:34)

Table 3 - Analysis populations - Cohorts B1 and B2

n (%)	Cohort B1 SAR444245 24 ug/kg + pembro (N=20)	Cohort B2 SAR444245 24 ug/kg + cetux (N=19)
Enrolled population	20	19
Exposed population	20 (100)	19 (100)
Population without trial impact (disruption) due to COVID-19	20 (100)	19 (100)
Efficacy population	20 (100)	19 (100)
PDy population	20 (100)	19 (100)

Percentages are calculated using the number of participants exposed as denominator

Extraction date: 11OCT2023

PGM=PRODOPS/SAR444245/ACT16903/CSR/REPORT/PGM/dis_ana_pop_a_t.sas
OUT=REPORT/OUTPUT/dis_ana_pop_b1b2_a_t_i.rtf (06FEB2024 7:34)

Diagnosis and criteria for inclusion:

For participants in Cohort A1- Histologically or cytologically confirmed diagnosis of HNSCC who are treatment-naïve for R/M disease, PD-L1 Combined Positive Score (CPS) ⩾1, and at least 1 measurable lesion per RECIST 1.1 criteria. No prior treatment systemic therapy for R/M disease, except systemic therapy as part of multimodal treatment for locally advanced disease if completed at least 6 months prior to enrollment.

For participants in Cohort B1- Histologically or cytologically confirmed diagnosis of R/M HNSCC previously treated with PD1/PD L1-based regimen & platinum-based regimen after failure of no more than 2 regimens for recurrent and/or metastatic (R/M) disease, and at least 1 measurable lesion per RECIST 1.1 criteria.

For participants in Cohort B2 - Histologically or cytologically confirmed diagnosis of R/M HNSCC previously treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease, and at least 1 measurable lesion per RECIST 1.1 criteria.

Study products

Investigational medicinal product(s):

SAR44425

Route(s) of administration: intravenous (IV) infusion.

Dose regimen: 24 µg/kg administered as an IV infusion over 30 mins every 3 weeks on Day 1 of each cycle (21 days per cycle) for up to 35 cycles or until PD.

Pembrolizumab

Route of administration: IV infusion.

Dose regimen: Pembrolizumab will be administered at a dose of 200 mg using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle for up to 35 cycles.

Cetuximab

Route of administration: IV infusion.

Dose regimen: cetuximab will be given on Cycle 1 Day 1 as an initial loading dose of 400 mg/m2 infused over 120 minutes (maximum infusion rate 10 mg/min or as per local practice and labels) followed by weekly 250 mg/m2 infused over 60 minutes (maximum infusion rate 10 mg/min) for all subsequent doses starting with the Cycle 1 Day 8 administration until progressive disease (PD).

Noninvestigational medicinal products (NIMPs)

Premedication for SAR444245:

All participants received the following premedication to prevent or reduce the acute effect of infusion-related reactions (IRR) or flu-like symptoms, 30 to 60 minutes prior to SAR444245 infusion (no longer than 60 minutes) for the first 4 cycles:

•Acetaminophen (paracetamol) 650 to 1000 mg IV or oral route (PO) (or equivalent), and then optionally thereafter, as needed.

•Diphenhydramine 25 to 50 mg IV or PO (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter, as needed.

SAR444245 premedication may have been optional after 4 cycles

•For a participant who had no IRR during the first 4 cycles: Premedication for the subsequent infusions was optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the participant experienced an IRR (any grade), premedication must have been restarted for all subsequent infusions.

•If a participant developed an IRR Grade <2 during their first cycle only and then experiences no further IRRs during their next 3 cycles: The Investigator considered omitting premedication for the next cycle. If no IRR was observed during the next cycle without premedication, premedication was optional for the subsequent cycles at the Investigator's discretion. However, if during the next cycle without premedication the participant experienced an IRR (any grade), premedication must have been restarted for all subsequent cycles.

Premedication for cetuximab:

All participants who received cetuximab should have been pre-medicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab, or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should have been given as per medical judgment and history of prior infusion reactions (IR).

When SAR444245 and cetuximab were given on the same day, participants who have received diphenhydramine as cetuximab premedication may skip the diphenhydramine as SAR444245 premedication.

Duration of study intervention:

Duration of treatment: the cycle duration was 21 days

Duration of observation;

•A Screening period: up to 28 days.

•A Treatment Period: up to 35 cycles.

•An End of Treatment and Follow-up period: End of Treatment Visit to occur 30 days from last IMP administration or prior to initiation of further therapy followed by an Observation period depending on the status of the participant:

-Participants who discontinued study treatment without PD or who completed 35 cycles of treatment without PD were to be followed every 3 months from last IMP administration, until PD, start of another anticancer therapy, final cohort cut-off, whichever occurred first.

-Participants who discontinued study treatment with PD were to be followed in the Follow-Up Visit 1 occurring 3 months from last IMP administration.

•Survival Phone Call Follow-Up Period: until death, participant requested to discontinue from follow-up, or final cohort cut-off, or upon cancellation of Survival Follow-up at the discretion of the Sponsor.

Criteria for evaluation:

Primary

•Objective response rate (ORR) defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary

•Incidence of TEAEs, SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading

•Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1

•Duration of Response (DOR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first

•Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1)

•Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of first documented disease progression determined by Investigator as per RECIST 1.1, or death due to any cause, whichever occurs first

•Plasma concentrations of SAR444245

•Incidence of anti-drug antibodies (ADAs) against SAR444245

Statistical methods:

This study was not intended to explicitly test a hypothesis, and calculations of power and Type I error were not considered in the study design. No formal testing procedure was planned.

Analysis populations

Exposed: All participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 + pembrolizumab or SAR444245 + cetuximab).

Efficacy: All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.

All efficacy analyses were to be performed on the efficacy population and analyzed by cohort. Objective response rate, as well as PFS, DOR, and CBR were derived using the local radiologist's/Investigator's assessment for all cohorts. The assessments for all cohorts will use RECIST 1.1.

The primary endpoint was the best overall response (BOR) observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anticancer therapy, whichever occurred first. The BOR was summarized with descriptive statistics. The Objective Response Rate (ORR) was summarized with descriptive statistics and the corresponding two sided 90% CIs calculated from Clopper Pearson exact method. All objective responses had to be confirmed by a subsequent assessment performed at least 4 weeks apart from the initial response observation.

All safety analyses were performed on the exposed population and were descriptive in nature.

All adverse events (AEs) were coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 26.0 and graded according to National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE version 5.0). Cytokine release syndrome (CRS) and Immune effector cell associated neurotoxicity syndrome (ICANS) were graded using the American Society for Transplantation and Cellular Therapy Consensus grading.

The primary AE analyses was on treatment-emergent adverse events (TEAEs), ie, AEs that occurred during the TEAE period, defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.

Summary Results:

Demographic and other baseline characteristics:

In 1L HNSCC Cohort A1 (SAR444245 + pembrolizumab), participants had a median age of 59.0 years, were predominantly male (90.0%), white (60.0%), and most had an ECOG PS score of 0 (12 [60.0%]) at baseline.

In 2/3L HNSCC Cohort B1 (SAR444245 + pembrolizumab), participants had a median age of 60.0 years, were predominantly male (80.0%), white (50.0%) and most had an ECOG PS score of 1 (17 [85.0%]) at baseline.

In 2/3L HNSCC Cohort B2 (SAR444245 + cetuximab), participants had a median age of 60.0 years (range: 33 to 75), were predominantly male (78.9%) and white (63.2%). ECOG score at baseline was 0 in 8 [42.1%]) participants and 1 in 11 [57.9%]) participants.

Exposure:

Of a total of 20 exposed participants in Cohort A1, the median duration of IMP exposure (SAR444245 and pembrolizumab) was 4.0 months, and the median cumulative dose of SAR444245 and pembrolizumab were 116 µg/kg and 1100 mg, respectively.

Of a total of 20 exposed participants in Cohort B1, the median duration of IMP and SAR444245 exposure was 2.1 months, and the median cumulative dose of SAR444245 and pembrolizumab were 72 µg/kg and 600.0 mg, respectively.

Of a total of 19 exposed participants in Cohort B2, the median duration of IMP and SAR444245 exposure was 4 months, and the median cumulative dose of SAR444245 and cetuximab were 121.3 µg/kg and 3389.6 mg/m2, respectively.

Anti-tumor activity

In Cohort A1, out of the 20 participants, 1 participant (5.0%) had a BOR of CR and 4 participants (20.0%) had a BOR of PR. Stable disease (SD) was the BOR in 5 of 20 participants (25.0%), and 8 participants (40.0%) had progressive disease. The ORR was 25% (5/20; 90% CI: 10.4% to 45.6%)

In Cohort B1, out of 20 participants, none achieved PR or CR . Stable disease was the BOR in 4 of 20 participants (20.0%), and 10 participants (50.0%) had progressive disease. The ORR was 0% (0/20; 90% CI: 0.0% to 13.9%).

In Cohort B2, out of 19 participants, 3 participants (15.8%) had a BOR of PR and none (0%) had a BOR of CR. Stable disease was the BOR in 9 of 19 participants (47.4%), and 6 participants (31.6%) had progressive disease. The ORR was 15.8% (3/19; 90% CI: 4.4% to 35.9%).

Safety results:

As of the partial database lock date, the safety profile of SAR444245 in combination with pembrolizumab or cetuximab indicates that the treatment is generally manageable with standard therapies. Any observed variability in the nature of AEs between treatment regimens has been generally consistent with the known safety profile of cetuximab and pembrolizumab.

Of N=20 exposed participants in Cohort A1, all participants (100.0%) had a TEAE of any grade, 11 participants (55.0%) had a treatment-emergent SAE, 14 participants (70.0%) had a Grade ≥3 TEAE, 3 participants (15.0%) had a TEAE leading to permanent full intervention discontinuation, and 2 participants (10.0%) had a fatal Grade 5 TEAE. Serious treatment-related TEAEs were reported in 5 participants (25.0%) and treatment-related Grade ≥ 3 TEAEs were reported in 9 participants (45.0%).

Of N=20 exposed participants in Cohort B1, all participants (100%) had a TEAE of any grade, 11 participants (55.0%) had a treatment-emergent SAE, 9 participants (45.0%) had a Grade ≥3 TEAE, 4 participants (20.0%) had a TEAE leading to permanent full intervention discontinuation, and 3 participants (15.0%) had a fatal Grade 5 TEAE. Serious treatment-related TEAEs were reported in 5 participants (25.0%) and treatment-related Grade ≥ 3 TEAEs were reported in 2 participants (10.0%).

Of N=19 exposed participants in Cohort B2, all participants (100.0%) had a TEAE of any grade, 8 participants (42.1%) had a treatment-emergent SAE, 16 participants (84.2%) had a Grade ≥3 TEAE, 3 participants (15.8%) had a TEAE leading to permanent full intervention discontinuation, and 3 participants (15.8%) had a fatal Grade 5 TEAE. Serious treatment-related TEAEs were reported in 2 participants (10.5%) and treatment-related Grade ≥3 TEAEs were reported in 8 participants (42.1%).

The nature, frequency and severity of TEAEs showed no apparent disproportionality across cohorts. The most frequently reported TEAEs were pyrexia and CRS, reported in 35.0% of participants in Cohort A1, pyrexia reported in 35.0% of participants in Cohort B1, while for Cohort B2 the most frequently reported TEAE was nausea in 42.1% of participants. Other most frequently reported TEAEs by PT (≥30.0% of participants)were asthenia, nausea, vomiting in Cohort A1, fatigue in Cohort B1, and dermatitis acneiform, diarrhea and fatigue in Cohort B2.

The most frequently reported Grade ≥3 events were cardiac respiratory arrest and alanine aminotransferase increased (reported in 2 participants in Cohort A1), cardiac arrest (reported in 2 participants in Cohort B2). All other Grade ≥3 events were reported in 1 participant each across the cohorts.

The most frequently reported TEAEs related to any IMP were CRS, and pyrexia in Cohort A1, pyrexia, CRS, and fatigue in Cohort B1, nausea, dermatitis acneiform, and fatigue in Cohort B2. The most frequently reported adverse events of special interest (AESIs) were CRS and COVID 19, and infusion-related reaction (IRR).

Two events of capillary leak syndrome were reported in the study. Both occurred in Cohort A1 and 1 was Grade ≥3. No events of anaphylaxis, ICANS or Hy’ s law have been reported.

Across all cohorts most of the fatal AEs were in context other than disease progression: 1 participant had acute respiratory failure, and 1 participant had respiratory failure. Most deaths during the TE period or posttreatment period were due to progressive disease.

Serious TEAEs were reported in approximately 42.1% to 55.0% of participants across the cohorts. The most frequently reported treatment-emergent SAE was CRS (3 participants overall in Cohort A1, and 5 participants in Cohort B1.

TEAEs leading to permanent full discontinuation were reported in approximately 15.0% to 20.0% of participants across the cohorts. Almost all TEAEs leading to permanent full treatment discontinuation were Grade ≥3 TEAEs. In Cohort A1, 2 participants had a TEAE of cardiac respiratory arrest leading to permanent full treatment discontinuation, while in Cohorts B1 and B2 TEAEs leading to permanent full discontinuation were reported in no more than 1 participant.

Particular attention was given to analyzing data on infusion reactions which were identified using coding lists for CRS, infusion-related reaction, flu-like symptoms, and other TEAEs considered by the Investigator as related to any IMP and that happened soon after the start of an infusion. The most frequently reported TEAEs in the IR category were CRS and IRR. TEAEs in the IR category by worst grade were predominantly Grade 2 and Grade 1. The most frequently reported IR symptom in Cohorts A1

and B1 was pyrexia, mostly low grade in intensity, and chills in Cohort B2. Most TEAEs in the IR category occurred on the day of infusion and were resolved within 1-3 days.

Across all cohorts, the most frequently reported hematological abnormalities during the TE period were anemia (≥90.0% of participants) and lymphocyte count decreased (30.0%, 50.0% and 57.9% of participants across Cohorts A1, B1, and B2 respectively). Anemia was primarily low grade. Lymphocyte count decreased was predominantly Grade 4 in intensity in Cohort A1 and Grade 2 in Cohorts B1 and B2.

Across all cohorts, no relevant clinically PCSA in renal function abnormality at baseline. During the TE period, 1 participant (5.3%) had an estimated glomerular filtration rate (eGFR)

≥15-<30 mL/min/1.73m^2 (severe impairment) in Cohort A1, and 2 participants in Cohort B1 (10.0%) and 1 participant Cohort B2 (5.3%) had an eGFR <15 mL/min/1.73m^2 (end stage renal disease), respectively.

In Cohort B2 only, at baseline, 1 out of 19 participants had an alkaline phosphatase (ALP) >10 - ≤20 ULN. During the TE period, increases in ALT, AST, and bilirubin that were PCSAs were reported in 1 to 4 participants each across all cohorts. PCSA increases in ALP were reported in >30.0% to 45.0% of participants in Cohorts B1 and B2.

While some PSCAs in laboratory parameters were observed during the TE period, all included plausible alternative etiologies and none required further actions for safety reason.

Other results:

Pharmacokinetic and immunogenicity data were not available at the time of database lock and will be presented separately.

Issue date: 29-Apr-2025