

Sponsor: Sanofi Drug substance(s): SAR444245 - pegenzileukin	Study Identifiers: IND: 153865 EudraCT/EU trial number: 2020-005332-30 NCT: NCT04913220 WHO: U1111-1254-0189 Study code: ACT16845
Title of the study: A Phase 1/2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR 707) combined with cemiplimab for the treatment of participants with advanced unresectable or metastatic skin cancers	
Study center(s): 21 active centers in 7 countries (Australia, Chile, France, Germany, Italy, Spain, United States).	
Study period: Date first study participant enrolled: 15 July 2021 Date last study participant completed: 21 October 2022 Study Status: Terminated (Early discontinuation based on strategic sponsor decision not driven by any safety concerns).	
Phase of development: Phase1/Phase2	
Objectives: Primary: <ul style="list-style-type: none"> • To determine the antitumor activity of SAR444245 in combination with cemiplimab. Secondary: <ul style="list-style-type: none"> • To determine the recommended Phase 2 dose (RP2D) and to assess safety profile of SAR444245 when combined with cemiplimab. • To assess other indicators of antitumor activity. • To assess the concentrations of SAR444245 when given in combination with cemiplimab. • To assess the immunogenicity of SAR444245. • To assess active concentrations of cemiplimab when given in combination with SAR444245. 	
Methodology: This was a Phase 1/2, multi-cohort, uncontrolled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with the immune checkpoint inhibitor (ICI) cemiplimab in ICI-naïve participants with advanced, unresectable, or metastatic skin cancers. Two cohorts assessing SAR444245 in combination with cemiplimab were planned as followed: <ul style="list-style-type: none"> • Cohort A - participants with previously untreated locally advanced, unresectable or metastatic melanoma, planned to assess the investigational combination regimen as 1L therapy. • Cohort B - participants with ICI-naïve metastatic or locally advanced CSCC who were not candidates for curative surgery or curative radiation and who had received no more than 2 prior lines of systemic therapy. The study started with a dose escalation to determine the RP2D of SAR444245 when combined with cemiplimab. A minimum number of 3 DLT evaluable participants at each dose cohort and a minimum of 6 DLT-evaluable participants were to be treated at RP2D before starting the dose expansion. The Sponsor decided to terminate the study early for non-safety reasons as of 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 cemiplimab was lower than projected. The safety profile of SAR444245 in combination with cemiplimab was generally manageable, and no actions were taken for safety reasons.

Number of study participants (planned and analyzed):

Approximately 40 participants per cohort were initially planned to be enrolled and treated at the RP2D. The 2 treatment cohorts planned in the study were both initiated prior to the Sponsor's decision to terminate the study.

The actual number of participants analyzed per analysis population is shown in Table 1.

Table 1- Analysis populations

n (%)	Cohort A	Cohort A	Cohort B	Cohort B
	SAR444245 16	SAR444245 24	SAR444245 16	SAR444245 24
	ug/kg + cemi (N=20)	ug/kg + cemi (N=7)	ug/kg + cemi (N=16)	ug/kg + cemi (N=3)
Enrolled population	20	7	16	3
Exposed population	20 (100)	7 (100)	16 (100)	3 (100)
Population without trial impact (disruption) due to COVID-19	20 (100)	7 (100)	16 (100)	3 (100)
Efficacy population	20 (100)	7 (100)	16 (100)	3 (100)
DLT-evaluable population	5 (25.0)	7 (100)	4 (25.0)	3 (100)
PDy population	19 (95.0)	7 (100)	14 (87.5)	3 (100)

Diagnosis and criteria for inclusion:

The main inclusion criteria were:

For participants in Cohorts A: histologically-confirmed unresectable locally advanced or metastatic melanoma that are not amenable to local therapy, and at least one measurable lesion per RECIST 1.1 criteria.

For participants in Cohorts B: histologically-confirmed metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery and curative radiation, and at least one measurable lesion per RECIST 1.1 or at least a lesion that can be followed by serial digital medical photographs using modified WHO criteria.

The main exclusion criteria were:

Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≥ 2 and predicted life expectancy ≤ 3 months.

For participants in Cohorts A: diagnosis of uveal or ocular or desmoplastic melanoma.

For participants in Cohorts B: the primary site of CSCC was the dry red lip (vermillion) or the anogenital area (vulva, penis, scrotum, and perianal region) or mixed CSCC histologies (eg, sarcomatoid, adenosquamous).

Study products

Investigational medicinal product(s):

SAR444245:

Formulation/Form & composition: Infusion

Route(s) of administration: VI infusion

Dose regimen: every 3 weeks.

- dose escalation: 16 $\mu\text{g}/\text{kg}$ (DL1), 8 $\mu\text{g}/\text{kg}$ (DL-1), 24 $\mu\text{g}/\text{kg}$ (DL2).
- dose expansion: selected RP2D 16 $\mu\text{g}/\text{kg}$.

Cemiplimab:

Formulation/Form & composition: Infusion

Route(s) of administration: VI infusion

Dose regimen: 350 mg every 3 weeks.

Noninvestigational medicinal product(s)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 for the first 4 cycles:

- Acetaminophen (paracetamol) 650 to 1000 mg IV or oral route (PO), 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.
- Ondansetron 8 mg or 0.15 mg/kg IV (or equivalent eg, granisetron, dolasetron, tropisetron, palonosetron), and then optionally thereafter as needed.

SAR444245 premedication may have been optional after 4 cycles.

Duration of treatment/participation: 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 \pm 7 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 \pm 7 days 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: every 3 months and until death, participant request to discontinue from follow-up, or final cohort cut-off, or upon cancellation of Survival Follow-up at the discretion of the Sponsor.

In Cohort A SAR444245 16 μ g/kg + cemi, of the total of 20 exposed participants with previously untreated locally advanced, unresectable, or metastatic melanoma, 15 (75.0%) did not complete the study treatment and 5 (25.0%) were still receiving study intervention as of the partial database lock date (21 September 2023). At study completion, 4 out of 20 participants (20.0%) had completed the study treatment period, while remaining 16 out of 20 participants (80.0%) had permanent full intervention discontinuation, most commonly due to disease progression (8 participants [40.0%]), followed by adverse event (AE), not related to Coronavirus Disease 2019 (COVID-19) (7 participants [35.0%]). At the final database lock, no participants were on treatment.

In Cohort A SAR444245 24 μ g/kg + cemi, of the total of 7 exposed participants with previously untreated locally advanced, unresectable, or metastatic melanoma, 4 (57.1%) did not complete the study treatment and 3 (42.9%) were still receiving study intervention as of the partial database lock date (21 September 2023). At study completion, 2 out of 7 participants (28.6%) had completed the study treatment period, while remaining 5 out of 7 participants (71.4%) had permanent full intervention discontinuation, most commonly due to disease progression (4 participants [57.1%]). At the final database lock, no participants were on treatment.

In Cohort B SAR444245 16 μ g/kg + cemi, of the total of 16 exposed participants with previously untreated metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC), 10 (62.5%) did not complete the study treatment and 6 (37.5%) were still receiving study intervention as of the partial database lock date (21 September 2023). At study completion, 4 out of 16 participants (25.0%) had completed the study treatment period, while remaining 12 out of 16 participants (75.0%) had permanent full intervention

discontinuation, most commonly due to AE, not related to COVID-19 (4 participants [25.0%]), followed by disease progression and withdrawal by subject (3 participants [18.8%], each]). At the final database lock, no participants were on treatment.

Criteria for evaluation:

Primary:

- **Cohort A** (melanoma): Objective response rate (ORR) defined as the 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.
- **Cohort B** (cutaneous squamous cell carcinoma): ORR defined as the proportion of participants who have a confirmed CR or PR determined by Investigator per RECIST 1.1, or modified World Health Organization (WHO) criteria for medical photographs of external skin lesions, or composite criteria.

Secondary:

- Incidence of TEAEs, dose limiting toxicities (DLTs), SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus gradings.
- Complete Response rate (CRR) defined as the proportion of participants who have a confirmed CR determined by Investigator per RECIST 1.1 for melanoma participants and when applicable for CSCC participants (CR in localized unresectable CSCC is exploratory).
- Time to CR 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 CR that is subsequently confirmed and determined by Investigator per RECIST 1.1 for melanoma participants and when applicable for CSCC participants.
- Time to Response (TTR) defined as the time from the first administration of 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 or modified WHO criteria or composite criteria, whichever relevant.
- Duration of Response (DOR), defined as the time from first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or modified WHO criteria for medical photographs or composite criteria when relevant, or death from any cause, whichever occurs first.
- Clinical Benefit Rate (CBR) including confirmed CR or PR at any time or stable disease of at least 6 months (determined by Investigator per RECIST 1.1 or modified WHO criteria for medical photographs or composite criteria whichever relevant).
- Progression Free Survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by Investigator per RECIST 1.1, or modified WHO criteria for medical photographs when relevant or death due to any cause, whichever occurs first.
- Concentration of SAR444245.
- Incidence of anti-drug antibodies (ADAs) against SAR444245.
- C_{trough} and $C_{\text{end_of_infusion}}$ of cemiplimab

Statistical methods:

This study was not intended to explicitly test a hypothesis, and calculations of power and Type 1 error were not considered in the study design. No formal testing procedure was planned.

Sample size

The study started with a dose escalation to determine the RP2D of SAR444245 when combined with cemiplimab in a sample of at least 3 DLT evaluable participants at each dose-cohort and at least 6 DLT-evaluable participants treated at RP2D. At the end of the dose escalation, the occurrence of DLT and other safety data were to be reviewed by SB to determine the RP2D.

Participants enrolled in the dose escalation and treated at the RP2D were included in the total number of participants. In the dose expansion approximately 40 participants were to be included and treated at the confirmed safe dose per cohort. Cumulative safety data were reviewed periodically by the Data Monitoring Committee (DMC).

Interim analysis

As planned in the SAP, informal interim analyses were conducted during the study for each cohort, after 20 participants at the confirmed safe dose had undergone 2 post-baseline tumor assessments or had discontinued study treatment, whichever occurred first. Based on the results of this interim analysis and of preliminary assessments performed on the other SAR444245 studies in the Phase 1/2 program which indicated that antitumor activity at the Q3W dosing regimen was below what was expected, the Sponsor decided to discontinue enrollment into the study.

Consequently, not all the analyses described in the SAP were performed. The abbreviated report provides efficacy data available as of the date of the partial database lock. The cohort cut-off for the primary ORR endpoint analyses was estimated to be approximately 9 months from the date of the last participant's first infusion in the dose expansion phase.

Analysis populations

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

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

DLT-evaluable: All exposed participants in the dose escalation who have been treated and observed for at least 21 days. Any participants who experienced a DLT during DLT observation period were also DLT-evaluable.

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 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. 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:

Population characteristics:

Demographic and other baseline characteristics:

In Cohort A 16 µg/kg + cemi, participants had a median age of 60.0 years, were predominantly male (65.0%), white (100.0%), and most had an ECOG PS score at baseline of 0 (85.0%).

In Cohort A 24 µg/kg + cemi, participants had a median age of 58.0 years, were almost equally male (57.1%) or female (42.9%), were predominantly white (85.7%) and had an ECOG PS score at baseline of 0 (85.7%).

In Cohort B 16 µg/kg + cemi, participants had a median age of 67.5 years, were predominantly male (68.8%), white (81.3%), and had an ECOG PS score at baseline of 0 (68.8%).

In Cohort B 24 µg/kg + cemi, participants had a median age of 83.0 years, were predominantly male (100.0%), white (66.7%), and had an ECOG PS score at baseline of 0 (33.3%) or 1 (66.7%).

Exposure:

Cohort A SAR444245 16 µg/kg: across participants with previously untreated locally advanced, unresectable, or metastatic melanoma (N=20 exposed participants), the median duration of investigational medicinal product (IMP) (SAR444245 16 µg/kg + cemiplimab) exposure was 4.8 months (range: 1 to 26 months). Half of participants (10 participants [50.0%]) were treated for at least 7 cycles. The median total cumulative dose of SAR444245 was 88.9 µg/kg (range: 16 to 560 µg/kg), with a median relative dose intensity of 99.9% (range: 69% to 102%). The median total cumulative dose of cemiplimab was 1925.0 mg (range: 350 to 12250 mg), with a median relative dose intensity of 99.3% (range: 69% to 100%).

Cohort A SAR444245 24 µg/kg: across participants with previously untreated locally advanced, unresectable, or metastatic melanoma (N=7 exposed participants), the median duration of IMP (SAR444245 24 µg/kg + cemiplimab) exposure was 10.3 months (range: 2 to 25 months). Five participants (71.4%) were treated for at least 9 cycles. The median total cumulative dose of SAR444245 was 176.0 µg/kg (range: 72 to 840 µg/kg), with a median relative dose intensity of 91.5% (range: 66% to 100%). The median total cumulative dose of cemiplimab was 5250.0 mg (range: 1050 to 12250 mg), with a median relative dose intensity of 98.7% (range: 93% to 100%).

Cohort B SAR444245 16 µg/kg: across participants with metastatic or locally advanced CSCC (N=16 exposed participants), the median duration of IMP (SAR444245 16 µg/kg + cemiplimab) exposure was 16.2 months (range: 1 to 26 months). Half of participants (8 participants [50.0%]) were treated for at least 21 cycles. The median total cumulative dose of SAR444245 was 160.0 µg/kg (range: 32 to 560 µg/kg), with a median relative dose intensity of 94.5% (range: 63% to 100%). The median total cumulative dose of cemiplimab was 7175.0 mg (range: 700 to 12250 mg), with a median relative dose intensity of 95.1% (range: 63% to 100%).

In Cohort B SAR444245 24 µg/kg, 3 participants were exposed; the median duration of exposure to IMP (SAR444245 and cemiplimab) was 4.8 months and the median cumulative doses of SAR444245 and cemiplimab were 48.1 µg/kg and 2450 mg, respectively. The median relative dose intensity of SAR444245 and cemiplimab were 83.1% (range: 33 to 93) and 93.3% (range: 92 to 101), respectively.

Anti-tumor activity:

In Cohort A, at the proposed SAR444245 RP2D dose of 16 µg/kg Q3W the ORR (confirmed CR or PR) was 40% (90% CI: 21.7 to 60.6) including 1 participant with CR and 7 participants with PR.

In Cohort B, at the proposed SAR444245 RP2D dose of 16 µg/kg Q3W, the ORR (confirmed CR or PR) was 56.3% (90% CI: 33.3 to 77.3) including 9 participants with PR.

Safety results:

As of the partial database lock date, the safety profile of SAR444245 in combination with cemiplimab indicates that the treatment is generally manageable with standard therapies.

At a SAR444245 dose of 16 µg/kg Q3W, of N=20 exposed participants in Cohort A, 20 (100.0%) participants had a TEAE of any grade, 13 (65.0%) participants had a Grade ≥3 TEAE, 10 (50.0%) participants had a treatment-emergent SAE, and 7 participants (35.0%) had a TEAE leading to permanent full treatment discontinuation. Serious treatment-related TEAEs were reported in 8 (40.0%) participants and Grade ≥3 treatment-related TEAEs were reported in 11 (55.0%) participants.

At a SAR444245 dose of 24 µg/kg Q3W, of N=7 exposed participants in Cohort A, 7 (100.0%) participants had a TEAE of any grade, 4 (57.1%) participants had a Grade ≥3 TEAE, 5 (71.4%) participants had a treatment-emergent SAE, and 1 participant (14.3%) had a TEAE leading to permanent full treatment discontinuation. Serious treatment-related TEAEs were reported in 3 (42.9%) participants and Grade ≥3 treatment-related TEAEs were reported in 4 (57.1%) participants.

At a SAR444245 dose of 16 µg/kg Q3W, of N=16 exposed participants in Cohort B, 16 (100.0%) participants had a TEAE of any grade, 9 (56.3%) participants had a Grade ≥3 TEAE, 8 (50.0%) participants had a treatment-emergent SAE, and 3 participants

(18.8%) had a TEAE leading to permanent full treatment discontinuation. Serious treatment-related TEAEs, and Grade ≥ 3 treatment-related TEAEs were each reported in 6 (37.5%) participants.

At a SAR444245 dose of 24 $\mu\text{g}/\text{kg}$ Q3W, of N=3 exposed participants in Cohort B, 3 (100.0%) participants had a TEAE of any grade, 2 (66.7%) participants had a Grade ≥ 3 TEAE, 1 (33.3%) participant had a treatment-emergent SAE, and 2 (66.7%) participants had a TEAE leading to permanent full treatment discontinuation. Serious treatment-related TEAEs, and Grade ≥ 3 treatment-related TEAEs were each reported in 1 (33.3%) participant.

A total of 5 DLT events occurred across cohorts, of which, 3 were of Grade ≥ 3 . In Cohort A, 1 DLT of Grade ≥ 3 thrombocytopenia was reported in a participant at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$ Q3W. In Cohort B, DLTs of Grade ≥ 3 ALT and AST increased were reported in 1 participant at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$ Q3W, and 1 DLT of Grade ≥ 3 IRR was reported in a participant at SAR444245 dose of 24 $\mu\text{g}/\text{kg}$ Q3W.

The nature, frequency, and severity of TEAEs showed no apparent disproportionality across cohorts. Across all 4 cohorts, the most frequently reported TEAE was infusion-related reaction. In Cohort A, IRR was reported in 65% and 71.4% of participants at SAR444245 doses of 16 $\mu\text{g}/\text{kg}$ and 24 $\mu\text{g}/\text{kg}$, respectively. In Cohort B, IRR was reported in 87.5% and 100% of participants at SAR444245 doses of 16 $\mu\text{g}/\text{kg}$ and 24 $\mu\text{g}/\text{kg}$, respectively. Other most frequently reported TEAEs by PT (>10% of participants in all cohorts) included fatigue, pruritus, asthenia, cytokine release syndrome, diarrhoea, nausea, hypertension and weight decreased.

The most frequently reported Grade ≥ 3 events (as defined by having occurred in more than 1 study participant) were immune-mediated myocarditis (reported in 3 participants in Cohort A at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$), immune-mediated hepatitis and hypertransaminasaemia (each reported in 2 participants in Cohort A at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$), and thrombocytopenia and alanine aminotransferase increased (each reported in 2 participants in Cohort B at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$). Across all cohorts, 2 participants had Grade ≥ 3 event of infusion-related reaction.

Across all cohorts, the most frequently reported TEAEs related to any IMP were infusion related reaction, cytokine release syndrome, fatigue, and diarrhoea. The most frequently reported AESIs were infusion-related reaction, cytokine release syndrome, and Covid-19.

Across all cohorts, 2 participants in Cohort A at a SAR444245 dose of 16 $\mu\text{g}/\text{kg}$ Q3W had a fatal AE in context other than disease progression: 1 participant had immune-mediated myocarditis, and 1 participant had pulmonary embolism. One death occurred during the TE period due to an adverse event. Most deaths during the post-treatment period were due to progressive disease.

Treatment-emergent SAEs were reported in approximately 33.3% to 71.4% of participants across the cohorts. The most frequently reported treatment-emergent SAE were infusion related reaction (3 participants in Cohort B, 2 participants at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$ and 1 participant of 24 $\mu\text{g}/\text{kg}$), immune-mediated myocarditis (3 participants in Cohort A at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$), and cytokine release syndrome (3 participants in Cohort A at SAR444245 dose of 24 $\mu\text{g}/\text{kg}$, 1 participant in Cohort A at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$ and 1 participant in Cohort B at SAR444245 dose of 16 $\mu\text{g}/\text{kg}$).

TEAEs leading to permanent full treatment discontinuation were reported in approximately 14.3% to 66.7% of participants across the cohorts. Almost all TEAEs leading to permanent full treatment discontinuation were Grade ≥ 3 TEAEs. Across the cohorts, no participant had a TEAE of cytokine release syndrome leading to permanent full treatment discontinuation.

Particular attention was given to analyzing data on infusion reactions which were identified using coding lists for cytokine release syndrome, 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 infusion reaction category were infusion-related reaction and cytokine release syndrome. TEAEs in the infusion reaction category by worst grade were predominantly Grade 2 and Grade 1. The most frequently reported infusion reaction symptom in each cohort was pyrexia, all low grade (Grade 1 or Grade 2) in intensity. Most TEAEs in the infusion reaction category occurred on the day of infusion and resolved within 3 days.

Across all cohorts, the most frequently reported hematological abnormalities (>70% of participants) during the TE period were lymphocyte count decreased and anemia. Lymphocyte count decreased was predominantly Grade 4 in intensity and in most participants was not present at baseline. Anemia was primarily low grade.

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.

No events of immune effector cell associated neurotoxicity syndrome (ICANS), capillary leak syndrome, anaphylaxis or Hy's law were reported in the study.

Safety follow-up results:

The cumulative safety data and safety follow-up data indicate that treatment with SAR444245 in combination with cemiplimab generally remains manageable with standard therapies.

Melanoma Cohorts A

SAR444245 16 µg/kg + cemiplimab Q3W

Out of 20 exposed participants at a SAR444245 dose of 16 µg/kg Q3W, all 20 participants (100.0%) had a treatment-emergent adverse event (TEAE) of any grade, 14 participants (70.0%) had a Grade ≥ 3 TEAE, 11 participants (55.0%) had a treatment-emergent (TE) serious adverse event (SAE), 7 participants (35.0%) had a TEAE leading to permanent full treatment discontinuation, no participant had TEAE leading to permanent partial treatment discontinuation, and 1 participant (5.0%) had Grade 5 TEAE. Serious treatment-related TEAEs were reported in 9 participants (45.0%) and Grade ≥ 3 treatment related TEAEs were reported in 12 participants (60.0%).

One participant had Grade ≥ 3 TEAE of prerenal failure as compared to none since the primary CSR cut-off. The Grade ≥ 3 event of prerenal failure was treatment-related and treatment emergent SAE. There were no additional participants who experienced a TEAE leading to permanent full treatment discontinuation, TEAE leading to permanent partial treatment discontinuation, and Grade 5 TEAE since the primary CSR cut-off date. One participant had a Grade 5 post-treatment AE (sudden cardiac death) as compared to none since the primary CSR cut-off.

The most frequently reported ($\geq 15\%$) all-grade-TEAEs by preferred term (PT) were infusion related reaction (13 participants [65.0%]), pruritus (6 participants [30.0%]), hypertension and diarrhea (5 participants [25.0%], each), asthenia, cytokine release syndrome, and nausea (4 participants [20.0%], each), decreased appetite, myalgia, COVID-19, urinary tract infection, immune-mediated hypothyroidism, immune mediated myocarditis, fatigue, and chills (3 participants [15.0%], each). Since the primary CSR cut-off, diarrhea was included among the most frequently reported all-grade-TEAEs.

Out of 20 exposed participants, 15 participants (75.0%) had at least 1 TEAE in the infusion reaction (IR) category. The most frequently reported TEAEs were infusion related reaction (13 participants, 65.0%) and cytokine release syndrome (4 participants, 20.0%). No events of anaphylaxis were reported. No additional participant was reported with TEAEs in the IR category since the primary CSR cut-off.

No additional participant had dose-limiting toxicities (DLTs) during the DLT observation period and TE adverse event of special interest (AESI) since the primary CSR cut-off.

SAR444245 24 µg/kg + cemiplimab Q3W

Out of 7 exposed participants at a SAR444245 dose of 24 µg/kg Q3W, all 7 participants (100.0%) had a TEAE of any grade, 4 participants (57.1%) had a Grade ≥ 3 TEAE, 4 participants (57.1%) had a treatment-emergent SAE, 1 participant (14.3%) had a TEAE leading to permanent full treatment discontinuation, and 1 participant (14.3%) had a TEAE leading to permanent partial discontinuation of SAR444245. Serious treatment-related TEAEs were reported in 3 participants (42.9%) and Grade ≥ 3 treatment-related TEAEs were reported in 4 participants (57.1%).

Since the primary CSR cut-off, there had been 1 less participant with a treatment emergent SAE. Initially, 1 participant was reported to have postoperative wound infection classified as an SAE. However, in the final database lock, this event was reclassified as an AE. One participant had a Grade ≥ 3 TEAE of lipase increased as compared to none since the primary CSR cut-off. There were no additional participants who experienced any Grade ≥ 3 TEAE, Grade ≥ 3 treatment related TEAEs, TEAE leading to permanent full

treatment discontinuation, TEAE leading to permanent partial treatment discontinuation, and serious treatment related TEAEs since the primary CSR cut-off date.

At a SAR444245 dose of 24 µg/kg Q3W, the most frequently reported (≥15%) all-grade-TEAEs by PT were infusion related reaction (5 participants [71.4%]), asthenia (4 participants [57.1%]), cytokine release syndrome and influenza like illness (3 participants [42.9%], each), diarrhea, nausea, weight decreased, nasopharyngitis, vitiligo, alanine aminotransferase increased, aspartate aminotransferase increased, and blood bilirubin increased (2 participants [28.6%], each). There were no changes in the most frequently reported (≥15%) all grade TEAEs by PT since the primary CSR data cut-off.

At SAR444245 dose of 24 µg/kg Q3W, 7 of 7 exposed participants (100.0%) had at least 1 TEAE in the IR category. The most frequently reported TEAEs were infusion related reaction (5 participants, 71.4%) and cytokine release syndrome and flu-like symptoms (3 participants each, 42.9%). No events of anaphylaxis were reported. Since the primary CSR cut-off, 2 additional events of amylase increased and hyperchloremia were reported (1 participant each).

No additional participant had DLTs during the DLT observation period and TE AESI since the primary CSR cut-off.

Cutaneous squamous cell carcinoma Cohorts B

SAR444245 16 µg/kg + cemiplimab Q3W

Out of 16 exposed participants at a SAR444245 dose of 16 µg/kg Q3W, all 16 participants (100.0%) had a TEAE of any grade, 10 participants (62.5%) had a Grade ≥3 TEAE, 8 participants (50.0%) had a treatment-emergent SAE, 3 participants (18.8%) had a TEAE leading to permanent full treatment discontinuation, and 5 participants (31.3%) had a TEAE leading to permanent partial discontinuation of SAR444245. Serious treatment-related TEAEs, and Grade ≥3 treatment-related TEAEs were each reported in 6 participants (37.5%).

One participant had a Grade ≥3 TEAE of hypertension as compared to none since the primary CSR cut-off. There were no additional participants who experienced any treatment emergent SAE, serious treatment related TEAEs, TEAE leading to permanent full treatment discontinuation, TEAE leading to permanent partial treatment discontinuation, and Grade ≥3 treatment-related TEAEs since the primary CSR cut-off date.

At a SAR444245 dose of 16 µg/kg Q3W, the most frequently reported (≥15%) all-grade-TEAEs by PT were infusion related reaction (14 participants [87.5%]), fatigue (6 participants [37.5%]), xerosis and stomatitis (5 participants [31.3%], each), nausea and pruritus (4 participants [25.0%], each), cytokine release syndrome, hypertension, weight decreased, decreased appetite, dizziness, arthralgia, and diarrhea (3 participants [18.8%], each). Since the primary CSR cut-off, diarrhea, nausea, and arthralgia were included among the most frequently reported all-grade-TEAEs.

At SAR444245 dose of 16 µg/kg Q3W, 16 of 16 exposed participants (100.0%) had at least 1 TEAE in the IR category. The most frequently reported TEAEs were infusion related reaction (14 participants, 87.5%) and cytokine release syndrome (3 participants, 18.8%). No events of anaphylaxis were reported. No additional participant was reported with TEAEs in the IR category since the primary CSR cut-off.

No additional participant had DLTs during the DLT observation period and TE AESI since the primary CSR cut-off.

SAR444245 24 µg/kg + cemiplimab Q3W

At SAR444245 dose of 24 µg/kg Q3W, there were no changes observed for the safety data since the primary CSR cut-off.

Pharmacokinetic results:

SAR444245 median concentrations at the end of infusion (C_{eo}) ranged from 200 to 414 ng/mL. Overall, SAR444245 concentrations in plasma were in the expected range for the dose administered. No signs for interferences of co-administered drugs on SAR444245 concentrations were observed.

Immunogenicity results:

In Cohort A SAR444245 16 µg/kg + cemi and in Cohort B SAR444245 24 µg/kg + cemi, there were no participants with treatment-emergent ADAs.

In Cohort A SAR444245 24 µg/kg + cemi, a treatment emergent ADA incidence of 14.3% was reported. One participant (100%) with treatment induced ADA showed persistent ADA response.

In Cohort B SAR444245 16 µg/kg + cemi, a treatment emergent ADA incidence of 8.3% was reported. One participant with treatment induced ADA showed an indeterminate ADA response.

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