NCT Number: NCT04913220

AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**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**
Protocol number:	**ACT16845**
Amendment number:	**04**
Compound number: (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with cemiplimab for the treatment of participants with various advanced skin cancers**
Acronym:	**Pegathor Skin 201**
Study phase:	**Phase 1/2**
Sponsor name:	**Sanofi Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifier number(s):

IND:	153865
EudraCT:	2020-005332-30
WHO:	U1111-1254-0189

Date:	20-Oct-2021	Total number of pages: 161

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	ALL	20 October 2021, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 03	ALL	25 August 2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 02	ALL	04 May 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	ALL	19 March 2021, version 1 (electronic 2.0)
Original Protocol		24 February 2021, version 1 (electronic 1.0)

Amended protocol 04 (20 October 2021)

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to meet German requirements to be consistent with the German GCP ordinance (§ 12 (4) GCP-V). Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page and 1.1 Synopsis	The following study name: “Pegasus” has been removed from the protocol title and changed to “Pegathor” on the title page.	Harmonization per program-level approach
1.1 Synopsis, 6.1.2 Non-investigational medicinal product	Oral administration of diphenhydramine is now permitted, in addition to IV administration. Intravenous administration of acetaminophen is now permitted, in addition to oral administration.	To allow local approved dosing regimens to be followed
1.2 Schema, 1.3 Schedule of activities (SoA), 1.4 Biomarker flowcharts, 5.1 Inclusion criteria	In Figure 2 and in the biomarker flowchart, tumor tissue collection has been removed from C1D15 and C2D8 and added on C2D1. In the SoA, footnote “f” for blood draws and/or tumor biopsy for biomarker assessment has been removed and changed to: ”Study Board may decide to cancel safety assessment on C1D15, upon agreement with Sponsor, if safety data justifies it.” The reference to the footnote “f” has been deleted at C1D8 in the SoA.	To make operational procedures easier

Section # and Name	Description of Change	Brief Rationale
	Inclusion criterion I06 has been revised to:" One biopsy on treatment is mandatory for participants in Cohort B, if clinically feasible".	
[redacted]	[redacted]	[redacted]
5.2 Exclusion Criteria	E 20 was changed from "Known hypersensitivity to or contraindication for the use of any study intervention, including premedication to be administered in this study, as well as PEG or any pegylated drug" to "Known hypersensitivity to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein".	To clarify that patients with known hypersensitivity to any excipient of the study interventions and hypersensitivity to any E. coli-derived protein must be excluded
5.2 Exclusion criteria, 6.5.2 Prohibited concomitant medications, 10.14 Appendix 14, and Risk assessment Table 12	[redacted] The following sentence in Section 6.5.2 has been deleted: "[redacted] In Table 12, the row for [redacted] was deleted.	Based on new de-risking in-vitro data
5.4 Screen failures	The following text was added "A participant may be rescreened only once".	For clarity
6.2 Preparation/handling/storage/accountability	The text was revised as shown below Under no circumstances will the Investigator supply IMP to a third party ~~(except for DTP shipment, for which a courier company has been approved by the Sponsor)~~, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.	Direct-to-patient shipment of IMP is not possible in this study.

Section # and Name	Description of Change	Brief Rationale
6.6.4.5 Immune cell-associated neurotoxicity syndrome (ICANS)	For clarity and brevity, command language has been used in Table 7.	Harmonization per program-level approach
	In Table 7 the following text has been added under Grade 3 ICANS: "Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 5. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days."	Harmonization per program-level approach
8.3.1 Time period and frequency for collecting AE and SAE information	The instruction to stop collecting AE and SAE information should the participant initiate another anticancer therapy was removed. All AEs and SAEs/AESIs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards
8.3.1 Time period and frequency for collecting AE and SAE information, 10.3.4 Reporting of SAEs 10.7 Country-specific requirements (Germany)	In Section 10.7, specific wording for the sites in Germany has been added indicating that "the Investigator must inform the Sponsor in case of a SAE/AESI immediately, after becoming aware without undue delay". Reference to Appendix 7 for country-specific requirements for Germany has been added in Sections 8.3.1 and 10.3.4.	Regulatory Authority (BfArM) request
10.14 Appendix 14: Risk assessment and 10.16 Appendix 16: Abbreviations	The text "SAR444245 infusion-associated reaction" was changed to "SAR444245 infusion-related reaction".	For consistency
Throughout the document	Minor editorial updates.	For clarity and consistency

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: 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

Brief title: A study of SAR444245 combined with cemiplimab for the treatment of participants with various advanced skin cancers

Rationale:

SAR444245, with its site-specific pegylation, was designed to substantially reduce association with the interleukin (IL)-2 α receptor, while retaining stimulatory activity for cells expressing the moderate affinity IL-2 βγ receptor. Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and non-human primate (NHP) models while anti-PD1 antibody prevents T cell suppression through the programmed cell death-1/programmed cell death-ligand 1 (PD1/PD-L1) pathway. The combination of anti-PD1 treatment with SAR444245 was tested in the syngeneic murine colon cancer Ct-26 model and induced enhanced anti-tumor activity demonstrated as an increased number of complete responses (CR) and tumor-free surviving animals compared to each agent given in monotherapy. These data support evaluation of SAR444245 in combination with an anti-PD1 antibody.

The proposed study aims to establish proof-of-concept that combining the anti-PD1 monoclonal antibody cemiplimab with the non-alpha IL-2 SAR444245 will result in a significant increase in the percentage of immune checkpoint inhibitors (ICI)-naïve patients with melanoma and cutaneous squamous cell carcinoma (CSCC) experiencing an objective response.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with cemiplimab.	• **Cohort A** (melanoma): Objective response rate (ORR) defined as the proportion of participants who have a confirmed CR or partial response (PR) determined by Investigator per response evaluation criteria in solid tumors (RECIST) 1.1 (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.

Objectives	Endpoints
Secondary	
• To determine the recommended Phase 2 dose (RP2D) and to assess safety profile of SAR444245 when combined with cemiplimab	• Incidence of treatment-emergent adverse event (TEAEs), dose limiting toxicities (DLTs), 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 gradings (2)
• To assess other indicators of antitumor activity	• 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 RECIST1.1 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 (SD) 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.
• To assess the concentrations of SAR444245 when given in combination with cemiplimab	• Concentration of SAR444245

Objectives	Endpoints
• To assess the immunogenicity of SAR444245	• Incidence of anti-drug antibodies (ADAs) against SAR444245
• To assess active concentrations of cemiplimab when given in combination with SAR444245	• C_{trough} and $C_{end\_of\_Infusion}$ of cemiplimab
Exploratory	
[redacted]	

Overall design:

This is a Phase 1/2, multi-cohort, un-controlled, 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.

SAR444245 and cemiplimab will be administered every 3 weeks in 21-day cycles.

The study includes 2 treatment cohorts:

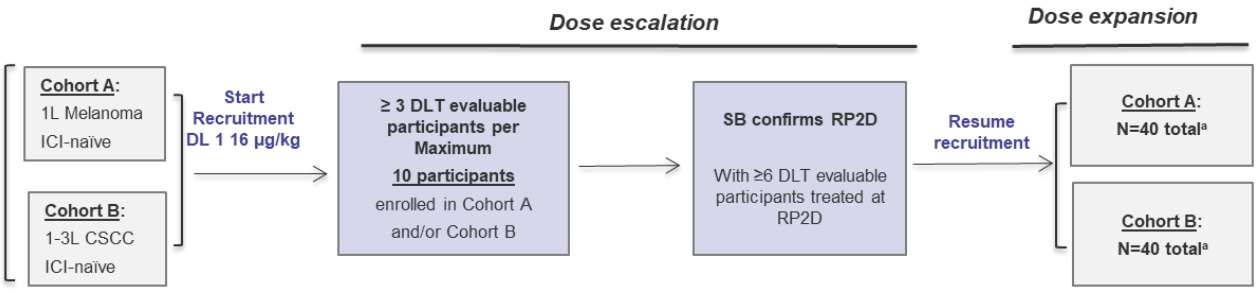
Cohort A will include approximately 40 participants with previously untreated **locally advanced, unresectable or metastatic melanoma**, and will assess the investigational combination regimen as first-line (1L) therapy.

Cohort B will include approximately 40 participants with ICI-naïve **metastatic CSCC or locally advanced CSCC** who are not candidates for curative surgery or curative radiation and who have received no more than 2 prior lines of systemic therapy.

The study will start with a dose escalation to determine the RP2D of SAR444245 when combined with cemiplimab. The starting dose will be 16 µg/kg Q3W (DL1) with a possibility to de-escalate to 8 µg/kg Q3W (DL -1) or escalate to 24 µg/kg Q3W (DL2) based on the occurrence of DLT and overall assessment of safety. The plan is to treat a minimum number of 3 DLT evaluable participants at each dose-cohort and a minimum of 6 DLT-evaluable participants treated at RP2D will be needed before starting the dose expansion. During the dose escalation, decision for next dose level (de-escalate, stay, escalate) will occur after the last patient has completed the DLT observation period (first 21 days) for the previous dose level. The Study Board (SB) will review DLT and overall safety data for these participants and will make the next dose recommendation. DLT-evaluable participants include all participants in the dose escalation who have been treated and observed for at least 21 days. Any participant who experienced a DLT during the first 21 days will also be DLT-evaluable. The determination of RP2D will be made by the SB after a minimum of 6 DLT-evaluable participants have been treated at this selected dose. Participants enrolled in the dose escalation and treated at the RP2D will be included in the total number of participants.

A graphical presentation of the study schema is shown in Figure 1.

Figure 1 - Overall study schema



[a] Total number including participants in dose escalation at the RP2D.
1L: first line;1-3L: first to third line CSCC: Cutaneous Squamous Cell Carcinoma; DLT: dose-limiting toxicity; ICI: immune checkpoint inhibitor; N: number of participants; SB: Study Board.

The DLT observation period is 21 days and will take into account the occurrence of DLT. The dose escalation will follow modified toxicity probability interval 2 (mTPI2**)** design.

Dose limiting toxicity: Selected events occurring during the DLT observation period (21 days of first cycle) are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245. Please refer to the full list of events in Section 4.1.

Special considerations pertaining to methodology

Interactive Response Technology will be used to control recruitment, assignment per site and facilitate drug supply.

Number of participants:

Overall, approximately 80 participants will be enrolled and treated at the RP2D.

Note: Enrolled participants are all participants from those screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Intervention groups and duration:

The duration of the study for a participant will include:

- **Screening period**: up to 28 days.
- **Treatment Period**: enrolled participants will receive continuous treatment until PD, unacceptable AE, other full permanent discontinuation criteria as described in Section 7, or completion of Cycle 35.
- **End of Treatment and Follow-up.** End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to end of treatment (**EOT)**:
    1. Participants who discontinue study treatment **without radiological or clinical PD** or who **complete 35 cycles of treatment without PD** (per RECIST 1.1 or modified WHO Criteria for medical photographs), will be followed for safety (as per Schedule of Activities [SoA]) and tumor imaging assessments every 3 months ±7 days from last IMP administration, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.
    2. Participants who discontinue study treatment **with radiological or clinical PD** (per RECIST 1.1 or modified WHO Criteria for medical photographs) **or** [redacted] will be followed in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration, before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-Up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. However, updated survival status may be requested by the Sponsor at any time during the course of the study. Survival Phone Call Follow-Up will continue 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 at any prior timepoint.

The cohort cut-off for the primary ORR endpoint analysis is estimated to be approximately 9 months from the date of the last participant's first infusion (to document that last participant response is maintained for 6 months).

After the cohort cut-off date for the primary ORR analysis, participants can continue to receive IMP, if clinical benefit is observed, until full permanent discontinuation criteria described in Section 7 are met, and will continue to undergo all assessments as per the study schedule of activities.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 3 years from cohort last patient-in (LPI).

Study interventions

Dosing sequence for both Cohort A and Cohort B: [redacted]

Investigational medicinal products

SAR444245

SAR444245 will be given [redacted]

- **Formulation**: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles**.:
  - dose escalation: 16 µg/kg (DL1), 8 µg/kg (DL-1), 24 µg/kg (DL2)
  - dose expansion: RP2D

Study sites should make every effort to target infusion duration to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted.

Cemiplimab

Cemiplimab infusion will start [redacted]

- **Formulation**: Libtayo® (cemiplimab) is a concentrate for solution for infusion supplied in a single-dose vial 350 mg/7 mL (50 mg/mL), clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles.
- Route of administration: IV infusion.
- **Dose regimen**: 350 mg administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles**.

Beyond 35 cycles and outside of the frame of this clinical study, the Investigator may decide to pursue treatment with the anti-cancer treatment of his choice.

Noninvestigational medicinal products

Premedication for SAR444245

All participants will receive 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 (or equivalent), and then optionally thereafter, as needed.
- Diphenhydramine 25 to 50 mg IV or oral route (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 be optional after 4 cycles in the below scenarios:

- For a participant who has no IRR during the first 4 cycles premedication for the subsequent infusions is optional at the Investigator's discretion (based on participant medical history, disease characteristics and other TEAEs, for example but not limited to cytokine release syndrome (CRS), flu-like symptoms observed until Cycle 4, part or all premedication components may be omitted). However, if during the subsequent infusions without premedication the participant experiences an IR (any grade or other TEAEs that could be mitigated by any components of premedication), premedication must be restarted for all subsequent infusions.
- If a participant develops an IRR Grade <2 during their first cycle only and then experiences no further IRRs during their next 3 cycles the Investigator may consider omitting premedication for the next cycle. If no IRR is observed during the next cycle without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion (based on participant medical history, disease characteristics and other TEAEs, for example but not limited to CRS, flu-like symptoms observed until Cycle 4, part or all premedication components may be omitted). However, if during the next cycle without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent cycles.

Statistical considerations:

- **Analysis of primary endpoint:** Objective response rate (ORR) and best overall response (BOR) will be summarized for the efficacy population with descriptive statistics. In addition, two sided 90% CIs for ORR will be computed using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints:**
  - The complete response rate (CRR) will be assessed for melanoma participants and when applicable for CSCC participants.
  - The time to CR will be assessed on the subgroup of melanoma participants who achieved confirmed CR and when applicable for CSCC participants in the efficacy population.

- The TTR will be assessed on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
- The DOR will only be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
- The CBR will be estimated by dividing the number of participants with clinical benefit by the number of participants from the efficacy population.
- The PFS will be summarized on the efficacy population using Kaplan-Meier methods. The median PFS times and associated 90% CI will be provided.

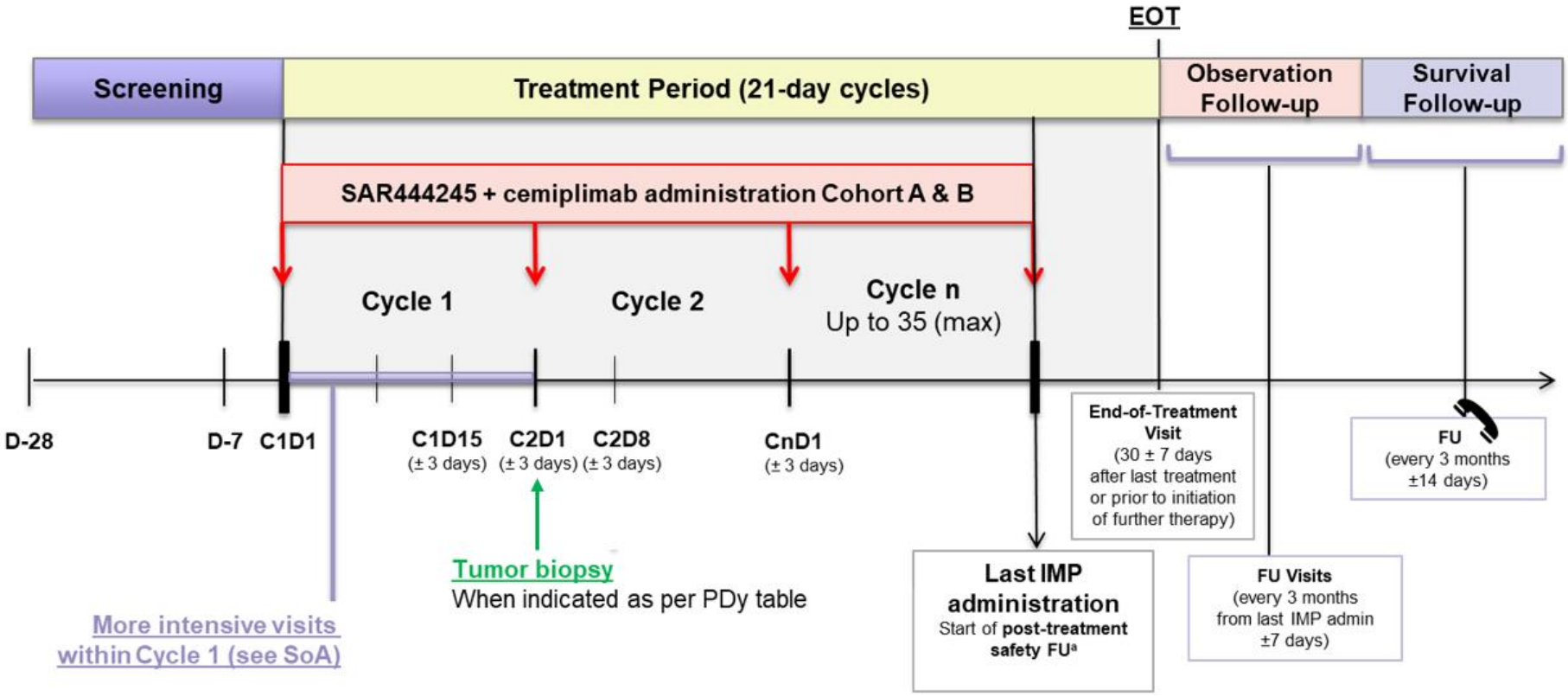
- **Analysis of secondary safety endpoints**
  - Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by primary System Organ Class (SOC) and PT will be summarized (all grades and Grade ≥3) for the exposed population. Similar summaries will be prepared for TEAEs related to SAR444245 and those related to cemiplimab, TEAEs leading to permanent partial intervention discontinuation (any of the IMP components), TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) and participants who died during study period (treatment, post-treatment) and reasons for death will be summarized. The NCI-CTCAE v 5.0 grading scale will be used for all events except cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), for which severity will be categorized using ASTCT consensus grading.
  - Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v 5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period will be provided for the exposed population.
- **Analysis of other secondary endpoints**
  - Concentrations of each cohort by SAR444245 and cemiplimab will be summarized with descriptive statistics.

Data Monitoring Committee: Yes.

Study Board: Yes. Details are provided in Section 4.1.

1.2 SCHEMA

Figure 2 - Graphical study design



a SAEs & AESIs collected throughout study period, from the signing of the informed consent form (ICF) until 90 days following last administration of study treatment OR until the participant initiates another anticancer therapy, whichever is earlier; AEs collected throughout study period, from the signing of the ICF until 30 days following last administration of study treatment OR until the participant initiates another anticancer therapy, whichever is earlier.

C: Study Cycle; D: Study Day; FU: Follow-Up; EOT: End-of treatment; PDy: Pharmacodynamic; IMP: Investigational medicinal product; SoA: Schedule of Activities.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]								End of Treatment	Observation Period[c]			Survival Phone Call FU[d]	Notes
		Cycle 1					Cycle 2	Cycles 3-6	Cycles 7-35	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone Call FU	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[e]**	**D8 (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months (±7 days) from last IMP admin**	**6 months (±7 days) from last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Informed consent	X														
IRT contact	X	X					X	X	X	X					
Inclusion and exclusion criteria	X														
Demography & Medical/Surgical & Disease History	X														See Section 8
PS (ECOG)	X	X			X	X	X	X	X	X	X				
Body Weight/Height[g]	X	X					X	X	X						
Full physical examination	X									X					See Section 8.2.1
Directed physical examination		X	X	X[e]	X	X	X	X	X	X	X				See Section 8.2.1

Evaluation[a]	Screening	Treatment Period[b]								End of Treatment	Observation Period[c]			Survival Phone Call FU[d]	Notes
		Cycle 1					Cycle 2	Cycles 3-6	Cycles 7-35	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone Call FU	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[e]**	**D8 (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months (±7 days) from last IMP admin**	**6 months (±7 days) from last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Vital Signs	X	X	X	X[e]	X	X	X	X	X	X	X				See Section 8.2.2
SpO2	X														
Laboratory and other investigations															
12-Lead ECG	X	As clinically indicated													See Section 8.2.3
LVEF	X	As clinically indicated													See Section 8.2.3
Troponin	X	As clinically indicated						X (D1 Cycle 4)	As clinically indicated						See Section 8.2.3 and Section 10.2
Pregnancy test	X	X					X	X	X	X	X	X			See Section 8.2.5 & Section 10.2
Hepatitis serology, CD4+ counts & HIV Viral Load	X	As clinically indicated													See Section 10.2
Hematology	X	X	X	X[e]	X	X	X	X	X	X	X				See Section 10.2

Evaluation[a]	Screening	Treatment Period[b]								End of Treatment	Observation Period[c]			Survival Phone Call FU[d]	Notes
		Cycle 1					Cycle 2	Cycles 3-6	Cycles 7-35	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone Call FU	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[e]**	**D8 (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months (±7 days) from last IMP admin**	**6 months (±7 days) from last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Coagulation	X	As clinically indicated													See Section 10.2
Blood Chemistry	X	X	X	X[e]	X	X	X	X	X	X	X				See Section 10.2
T3, FT4, TSH and cortisol	X						X	X	X	X	X				See Section 10.2
Urinalysis[h]	X	X						X	X	X	X				See Section 10.2
IMP		X					X	X	X						
Prior Medication	X														
Hospitalization[i]		X													
AE assessment[j]	X	Continuous throughout treatment period									X				See Section 8.3
Concomitant Meds	X	Continuous throughout treatment period													See Section 6.5
First subsequent anti-cancer therapy										X	X	X	X	X	
Survival status														X	
Pharmacokinetic (PK)/Pharmacodynamic (PDy)/Immunogenicity assessments															
PK SAR444245 and cemiplimab	See Pharmacokinetic Flow-Chart in Section 1.5														

Evaluation[a]	Screening	Treatment Period[b]								End of Treatment	Observation Period[c]			Survival Phone Call FU[d]	Notes
		Cycle 1					Cycle 2	Cycles 3-6	Cycles 7-35	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone Call FU	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[e]**	**D8 (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months (±7 days) from last IMP admin**	**6 months (±7 days) from last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
ADA SAR444245	See Pharmacokinetic Flow-Chart in Section 1.5														
PDy – Blood and tumor tissue collection	See Biomarkers Flow-Chart in Section 1.4														
Tumor assessment															
Brain imaging[k]	X	As clinically indicated													See Section 8.1.1
CT/MRI[l]	X							X	X	X	X	X	X		See Section 8.1.1
Digital medical photographs[m]	X							X	X	X	X	X	X		See Section 10.10
Tumor biopsies for CR confirmation (optional)[n]								X							

a **Evaluation**: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. Baseline evaluations should be completed within 7 days prior to the first dose of IMP, except for tumor assessment that may be performed within 28 days prior to IMP administration, and unless specified otherwise. There is no need to perform Cycle 1 Day 1 laboratory assessments that have been performed as part of screening within 3 days prior to C1D1. During the study treatment period, all assessments must be performed prior to IMP administration. Results should be reviewed by the Investigator prior to the administration of the next dose. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF can be signed more than 28 days prior to initiation of therapy and must be signed before any study-specific procedures. Screening time indicates the maximal time frame in which study procedures used to support eligibility are performed.

b **Cycle**: a treatment cycle is 21 days. IMP can be administered for up to 35 cycles. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the cycle number.

c **Observation Period**: Participants who enter the Observation period will be followed differently depending on the reason leading to permanent IMP discontinuation. See Section 4.1. For participant's convenience, all Follow-up assessments may occur during the same visit as that when imaging studies are obtained.

d **Survival Phone Call Follow-Up Period**: Participants who moves into the Survival Follow-up Phase should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study.

e Visit and assessments on C1D3 are only for participants in the dose escalation part.

f Study Board may decide to cancel safety assessment on C1D15, upon agreement with Sponsor, if safety data justifies it.

g **Weight/Height**: Height is required at baseline only. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

h **Urinalysis** will be performed every 4 cycles during Treatment period and as clinically indicated, at EOT and at follow-up visit 1.

i Only for dose escalation participants.

j Severity will be graded according to NCI-CTCAE v 5.0. ICANS and CRS will be graded using ASTCT criteria integrated with central laboratory cytokine results (2).

k **Brain imaging**: For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease. In all other cases, the lesions must be treated. Two additional scans, obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive therapy during these 4 weeks stabilization at the treating physician's discretion, it will be considered as part of prior anti-cancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least four weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain scan may be collected up to 42 days prior to enrollment.

l **CT/MRI**: The initial tumor imaging will be performed within 28 days prior to the date of enrollment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date first IMP administration or more frequently if clinically indicated. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment. After the first documentation of response per RECIST 1.1 or the first documentation of progression (if the participant is clinically stable), confirmatory imaging may be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anti-cancer therapy. Images (scans and/or photographs) and pathological reports when relevant for confirmation of CR or characterization of a new skin lesion in locally advanced CSCC will be prospectively collected for potential retrospective central analysis; the prospective collection of these materials can be cancelled at any time.

m **Digital medical photographs**: Tumor assessment for participants with externally visible CSCC lesions should be done using digital medical photographs according the modified WHO Criteria using an adequate camera platform.

n **Tumor biopsies**: For participants with externally visible CSCC lesions and objective response with visual or clinical CR, all effort should be made to collect a tumor biopsy in order to confirm CR, however, this biopsy remains optional. Tumor biopsies may also be done as deemed necessary to address special issues as per Appendix 10 (Section 10.11).

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; C=Cycle; CR=complete response; CSCC=cutaneous squamous cell carcinoma; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; FT4=free thyroxine; FU=Follow-Up; ICANS=Immune effector cell-associated neurotoxicity syndrome; ICF=Informed consent form; IMP=investigational medicinal product; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=progressive disease; PDy=pharmacodynamic; PK=pharmacokinetic; PS=Performance Status; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SpO2= oxygen saturation; T3=tri-iodothyronine; TSH=thyroid stimulating hormone; WHO=World Health Organization.

1.4 BIOMARKER FLOWCHART

The below flowchart applies to all participants in Cohort A and B. For participants in dose escalation, the plan is listed as below:

For participant enrolled in the dose escalation dose 16 µg/kg:

For participant enrolled in the dose escalation dose 24 µg/kg:

	Screening	Treatment period								End of treatment
Evaluation		**Treatment Cycle 1**					**Treatment Cycle 2**		**Treatment Cycle 4**	**EOT Visit**
Cycle day (sample collection window in Days)	**D-28 to -D1**	**D1**	**D2**	**D3**	**D8 (-1)**	**D15**	**D1 (-3)**	**D8**	**D1**	**30 (±7) days after last IMP administration**
[redacted]										

1.5 PHARMACOKINETIC FLOWCHART

The sampling time-points for PK and ADA for/against SAR444245 and/or other IMPs may be updated during the course of the study, based on the updated knowledge of drug behavior upon notification from the Sponsor.

1.5.1 All cohorts

Cycle	Treatment Cycle 1					Treatment Cycle 2, 4, 7, 10 + every 5th cycle		EOT visit
Day	**D1**		**D2**	**D3**[c]	**D15**	**D1**		
Time after start of SAR444245 dosing [h]	**SOI**	**EOI**	**At any time T24H**	**At any time T48H**	**At any time T360H**	**SOI**	**EOI**	**30 (±7) days after last IMP administration**
SAR444245 PK sample ID		P00[b]	P01	P02			P00[b]	
SAR444245 ADA sample ID	AB00[a]				AB01	AB00[a]		ABF00
Time after start of cemiplimab dosing [h]	SOI	EOI				SOI	EOI	
Cemiplimab PK sample ID	PC00[a]	PC01[b]				PC00[a]	PC01[b]	PCF00

a Samples collected strictly before start of infusion (SOI)
b P00 or PC01 samples = end of infusion (EOI) sample. Must be taken at EOI after flush.
c Only for participants in the dose escalation.
In case of overdose, ad-hoc PK sample should be collected right after an overdose is identified (only if identified within 5 days from start of overdose infusion).

Abbreviations: ADA: anti-drug antibodies, C: cycle; D: day; EOT: end of treatment; h: hour; PK: pharmacokinetic.

2 INTRODUCTION

SAR444245 is a recombinant human IL-2 with a site-specific substitution of a non-native azido lysine amino acid residue which is bio-conjugated to a single linear 30 kDa PEG. SAR444245 is being developed as an immuno-oncology treatment to be administered every 2 weeks (Q2W) or less frequently (every 3 weeks [Q3W] in the present study) in patients with cancer. [redacted]. The site-specific pegylation of IL-2 in SAR444245 provides a "non-alpha" pharmacologic profile for SAR444245 that is designed to prevent engagement of the high affinity IL-2Rα, while maintaining CD8+ T cell anti-tumor activity and resulting in an improved safety profile relative to aldesleukin. Aldesleukin is approved in the United States (US) for the following indications: the treatment of metastatic renal cell carcinoma (RCC) and metastatic melanoma, with the same or limited approval status in other countries. Its use has resulted in durable, CR in some patients with anti-tumor effects via elevations in CD8+ T cells (naïve, effector, and memory T cells). However, widespread use of aldesleukin is limited by its low response rate, short half-life (t1/2), and severe toxicities including primarily vascular leak syndrome (VLS), and cytokine release syndrome (CRS).

In contrast to native IL-2 and aldesleukin, SAR444245 does not have high potency at the IL-2Rα/β/γ receptor expressed on Treg cells because the site-specific pegylation blocks IL-2Rα engagement. Due to this re-programmed receptor bias, SAR444245 induces proliferation of peripheral CD8+ T and NK cells in vivo as observed in mice and NHP with negligible effect on the expansion of immunosuppressive Treg cells. Furthermore, SAR444245 does not bind IL-2Rα, and does not activate cells that express low levels of the high affinity IL-2Rα, such as Type 2 innate lymphoid cells (ILC-2s), eosinophils, and endothelial cells. Thus, it is expected to have a greatly reduced risk of VLS, and therefore a wider therapeutic window as compared to aldesleukin. In preclinical NHP studies, no signs of VLS were observed at a dose of SAR444245 that was [redacted] higher than the dose eliciting maximal expansion of peripheral CD8+ T cells. Therefore, in the clinic, SAR444245 is expected to have a wider therapeutic window as compared to aldesleukin due to a greatly reduced risk of VLS.

Furthermore, the site-specific pegylation extends the plasma $t_{1/2}$ of IL-2 in SAR444245 in mice and NHP to 9-13 h versus 85 min for aldesleukin in patients.

2.1 STUDY RATIONALE

Programmed cell death protein 1 inhibitors have emerged as one of the most important 1L treatment arsenal for various advanced and metastatic skin cancers. Pembrolizumab and nivolumab are approved for the treatment of 1L melanoma and cemiplimab, and more recently pembrolizumab are approved for the treatment of CSCC in the US. Despite the remarkable advance that PD1 inhibitors have brought to the treatment of these skin cancers, 50 to 60% of patients do not respond, and others will later progress (4, 5, 6, 7, 8, 9, 10, 11, 12).

SAR444245 is anticipated to potentiate PD1 inhibitors activity, thus leading to better response rate and/or better quality of response in both melanoma and CSCC, which should result in an improvement of the overall survival (OS) of the treated population. In preclinical studies, treatment with SAR444245 induced polyclonal expansion of CD8+ T cells in murine and NHP models while anti-PD1 antibody prevented T cell suppression through the PD1/PD-L1 pathway. The combination of anti-PD1 treatment with SAR444245 was tested in the Ct-26 colon cancer murine syngeneic tumor model, which is relatively resistant to anti-PD1 treatment, and demonstrated enhanced anti-tumor activity as well as prolonged survival compared to each agent administered alone.

These data support evaluation of SAR444245 in combination with a PD-1 inhibitor (SAR444245 Investigator's Brochure [IB]).

2.2 BACKGROUND

Melanoma and CSCC have always been described as immunogenic tumors. Indeed, patients who have undergone solid-organ transplantation and are receiving immunosuppressive therapy have a very significant risk of CSCC (13), suggesting that immune surveillance is critical for preventing CSCC in immunocompetent subjects.

Until recently, the standard of care (SoC) in metastatic melanoma was chemotherapy, which achieved a median survival time of about 6 months and 1-year OS of 25% (14). The only available immunological therapy was high-dose IL-2, which induced long-lasting responses only in a small subset of patients, and was associated with a high rate of severe toxicities (14).

Immune checkpoint inhibitors were the first class of therapy to show improved OS in patients with advanced melanoma, and the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab and the anti-PD-1 antibodies nivolumab and pembrolizumab are now the SoC in everyday clinical practice (15).

The introduction of ICIs, and in particular of anti-PD-1/PD-L1 therapeutic antibodies, has revolutionized the therapeutic paradigm not only in melanoma, leading to long-lasting responses in almost half of patients, but also in an increasing number of tumor types, including non-melanoma cancers (4, 5, 6, 7, 8, 9). Among these is advanced CSCC including locally advanced and metastatic CSCC not amenable to curative surgery or curative radiotherapy, or both. The prognosis is poor for patients with advanced CSCC treated with cytotoxic chemotherapy or epidermal growth factor receptor inhibitors, and is associated with substantial morbidity, impact on quality of life, and health care burden (16, 17, 18). The recent approval of cemiplimab in this indication has been a significant improvement in the care of these patients.

In the CheckMate-066 study, nivolumab alone proved superior to dacarbazine chemotherapy (51.2% 3-year survival compared to 21.6%). In CheckMate-067 and KEYNOTE-006 trials, nivolumab and pembrolizumab respectively proved superior to the anti-CTLA-4 ipilimumab; nivolumab induced a 3-year OS rate of 52% vs 34%, and pembrolizumab induced a 3-year OS rate of 48.1% vs 37.8% (8, 9, 5). In CheckMate-067 study, nivolumab combined to ipilimumab appeared superior to nivolumab alone (ORR 58% vs 44%; PFS 11.5 vs 6.9 months; OS 58% vs

52% OS at 3 years), although the study was not designed to demonstrate superiority of the combination. This apparent improvement in efficacy was obtained at the cost of higher toxicity (9, 19). Overall, from these clinical trials, ORR induced by ICI alone in 1L melanoma lays between 36% and 44%, indicating that approximately 60% patients fail to respond.

Advanced CSCC accounts for only 5% of all cases of CSCC but up to 60% of disease-related deaths (20). Until recently, there was no approved systemic therapy for patients with advanced CSCC. Substantial anti-tumor activity of cemiplimab with durable responses was demonstrated in both metastatic and locally advanced CSCC. Midgen et al. reported an ORR of 47% and 44% in the metastatic cohort and locally advanced cohort, respectively, leaving room for improvement (10, 11).

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of SAR444245 may be found in the IB.

2.3.1 Risk assessment

Safety data from clinical studies conducted with SAR444245 in human is currently limited to available safety data from the Phase 1/2 first-in-human (HAMMER) study. Consequently, the assessment of the risks associated to SAR444245 is also based on existing preclinical data, and takes into consideration the known safety profile of the structurally similar product aldesleukin (Proleukin®) and current knowledge of the new generation, investigational IL-2 analog NKTR-214 (bempegaldesleukin).

Risk assessment of SAR444245 and cemiplimab combination results therefore from anticipated risks for SAR444245 and from the label information for Libtayo® (cemiplimab), taking into account potential overlapping risks.

Table 12 summarizes potential risks for SAR444245 identified from preclinical experience and from the Phase 1/2 first-in-human (HAMMER) study, as well as available safety data for Libtayo, along with proposed mitigation strategies.

2.3.1.1 Aldesleukin experience

There is currently one marketed IL-2 product, Proleukin (aldesleukin). It is an IL-2 therapeutic that is currently licensed in the US for the treatment of metastatic RCC and metastatic melanoma and in several European countries for the treatment of metastatic RCC.

Aldesleukin is a human recombinant interleukin-2 which has been shown to possess the biological activities of human native IL-2 mediated through its binding with the high-affinity IL-2Rαβγ and intermediate-affinity IL-2Rβγ receptors. The widespread use of aldesleukin has been limited by its low response rate, a short $t_{1/2}$ that requires dosing three times per day, and toxicities (21), which include life-threatening and sometimes fatal VLS. Vascular leak syndrome is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. It results in hypotension and reduced organ perfusion which, if severe, can result in death. It may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Aldesleukin has been associated with exacerbation of pre-existing or initial presentation of auto-immune disease and inflammatory disorders. Exacerbation of Crohn's disease, scleroderma, thyroiditis, inflammatory arthritis, diabetes mellitus, oculo-bulbar myasthenia gravis, crescentic IgA glomerulonephritis, cholecystitis, cerebral vasculitis, Stevens-Johnson syndrome and bullous pemphigoid, have been reported following treatment with IL-2.

It was recognized early in clinical studies that eosinophilia appeared to mark the onset of VLS, with several reports of fast, dose-dependent elevation in eosinophils. Additional publications suggested a causal connection between the increase in peripheral IL-5 levels and identified ILC-2 as the source of this powerful chemoattractant and activator of eosinophils (22). Aldesleukin mediates activation of ILC-2s via interaction with the high affinity IL-2Rα chain that exists at low levels on ILC-2s.

Treatment with aldesleukin is associated with impaired neutrophil function (reduced chemotaxis) and the resulting increase in the risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of Proleukin therapy.

Proleukin toxicity threat mandates that it should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and cardiopulmonary or intensive care specialists must be available.

Proleukin has been shown to have embryolethal effects in rats but there are no adequate well-controlled studies in pregnant women; this information can be extrapolated to SAR444245. Also, since is not known whether SAR444245 is excreted in human breast milk, nursing mothers cannot participate to this study.

High doses of aldesleukin (IL-2) were associated with decreased expression of enzymes of hepatic metabolism (23). As SAR444245 also exercises IL-2 activity, the Investigator should monitor clinical effects of narrow therapeutic index drugs that are hepatically metabolized.

Please refer to Proleukin Label and SmPC for more detailed information.

2.3.1.2 SAR444245

2.3.1.2.1 Preclinical data

Among the potential risks, preclinical data for SAR444245 are lacking for infusion-related reactions (IRRs), immunogenicity (anti-drug antibodies), hypersensitivity, and immune-mediated adverse events. Those are, however, typical effects associated with the use of biologic drugs in oncology and should be considered for SAR444245.

Further, preclinical data for SAR444245 do not indicate the potential for nephrotoxicity, neurotoxicity or pulmonary toxicity, which are known adverse effects for aldesleukin. However, mitigation strategies for these risks are also proposed in the protocol.

Preclinical data for SAR444245 do not indicate higher risk for infections. However, infections are typically associated with the use of aldesleukin and are to be expected.

There are no preclinical data for tumor lysis syndrome (TLS) associated with the use of SAR444245, but it is known to occur when aldesleukin is combined with cisplatinum, vinblastine and dacarbazine (refer to Proleukin EU SmPC). The participants at greatest risk of TLS are those with high tumor burden prior to treatment, elevated uric acid level, poor hydration or tumor infiltration of the kidney, or receiving intensive cytoreductive therapy.

Cytokine release syndrome is a potentially life-threatening toxicity that has been described in the setting of immunotherapy with T-cell engagement. It is characterized by a variety of symptoms including high fevers, hypotension, rigors and malaise, and may progress to cytokine storm (uncontrolled immune hyperactivation involving myriad cytokines) with more severe and potentially life-threatening manifestations. As SAR444245 mediates immune activation, it may induce adverse events related to cytokine release (eg, fatigue, fever, chills, muscle pain, rash, nausea, symptoms of autoimmune disease). Furthermore, SAR444245-related increases of plasma monocyte chemoattractant protein-1 (MCP-1), IL-2, and IL-1RA were observed in non-human primates, indicating that SAR444245 administration may be associated with CRS.

No manifestations of VLS have been reported in pre-clinical toxicity studies with SAR444245. Although there is a theoretical risk of VLS occurring in an immunotherapy setting, it has not been observed for IL-2 variants with ‘non-alpha’ profiles. Being a ‘non-alpha’ IL-2, SAR444245 is not anticipated to cause VLS.

No data pertaining to pregnancy and lactation exposure and outcomes are available for SAR444245. Due to the missing information for this important risk, detailed mitigation measures will be introduced. Conditions for eligibility of women of reproductive potential and male subjects with female partners of childbearing potential are detailed in Section 5.1. Also, since is not known whether SAR444245 is excreted in human breast milk, nursing mothers cannot participate in this study.

2.3.1.2.2 Clinical studies

A Phase 1/2 first-in-human study (HAMMER) is currently ongoing in adult patients with advanced or metastatic solid tumors. This is an open-label, multicenter, dose escalation and expansion study of SAR444245 IV as a single agent and in combination with the checkpoint inhibitor pembrolizumab.

Available safety information from this study has informed the selection of the dose (see details in Section 4.3).

For the most up-to-date safety information from this study please refer to SAR444245 IB.

2.3.1.2.3 NKTR-214 (bempegaldesleukin) clinical data

Useful insight can also be obtained from NKTR-214 (bempegaldesleukin), another new generation IL-2 derivative, with activity biased towards the IL-2Rβγ receptor.

In the first-in-human Phase I study, NKTR-214 was administered as an outpatient regimen and was well tolerated. Twenty-eight patients with advanced or locally advanced solid tumor malignancies were enrolled in the study. Grade 3 treatment-related adverse events (TRAEs) were reported by 21.4% of patients; there were no Grade 4 TRAEs or any treatment related deaths. The most common TRAEs included fatigue (71%), flu-like symptoms (68%), pruritus (64%), hypotension (57%), rash (50%), decreased appetite (46%), arthralgia and cough (each 32%). The majority of these events coincided with the peak plasma concentrations of the active cytokine and resolved spontaneously or were mitigated by nonprescription oral or topical treatments. There was one reported immune-related adverse event (irAE) of hypothyroidism associated with NKTR-214, which was treated with replacement therapy. All Grade 3 hypotension events (18%) were rapidly reversed with IV fluid administration and did not require treatment discontinuation. NKTR-214-related hypotension was predictable, manageable, and reversible and the incidence of Grade 3 hypotension was reduced once hypotension risk mitigation strategies were implemented. The maximum tolerated dose (MTD) was determined to be 0.009 mg/kg Q3W. This new generation, IL-2Rβγ-biased IL2 could be safely administered as outpatient basis, and there was no report of capillary leak syndrome (CLS) or VLS (24).

In PIVOT-02, a single-arm, Phase I/II study, NKTR-214 plus nivolumab was administered to 38 patients with selected immunotherapy-naïve advanced solid tumors (melanoma, renal cell carcinoma, and non-small cell lung cancer). Several treatment regimens were explored. The dose of 0.009 mg/kg had excessive toxicity (2 of 3 patients with DLT: Gr 3 hypotension [n=1] & Gr 4 hyperglycemia + metabolic acidosis [n=1]) when combined with 360 mg of nivolumab. All 38 patients had TEAEs that were considered related to the study combination. The MTD of the combination was defined as NKTR-214 0.006 mg/kg + nivolumab 360 mg Q3 weeks and this dose was selected as the recommended Phase 2 dose (RP2D). The most common TRAEs (≥30%) at the RP2D were flu-like symptoms (80%), rash (80%), fatigue (76%), pruritis (48%), arthralgia (44%), headache, diarrhea (40%), nausea (40%), decreased appetite (36%) and peripheral edema (36%), myalgia (32%), and nasal congestion (32%). Grade ≥3 TRAEs occurred in 16% of patients at the RP2D (hyperglycemia, lipase increase, rash, cerebrovascular accident, hyponatremia, infectious pleural effusion, syncope). Immune-mediated AEs were observed in 31.6% overall: hypothyroidism (11), hyperthyroidism (2), hyperglycemia (2). Cytokine-related symptoms were

observed primarily in Cycles 1 & 2 and significantly reduced thereafter. There were no treatment-related deaths and generally, Grade ≥3 TRAEs were manageable using standard guidelines. Tumor responses were observed regardless of baseline PD-L1 status and baseline levels of tumor-infiltrating lymphocytes, suggesting therapeutic potential for patients with poor prognostic risk factors for response to PD1/PD-L1 blockade. These data demonstrated that NKTR-214 can be safely combined with a checkpoint inhibitor as dual immunotherapy for the treatment of a range of advanced solid tumors (25).

2.3.1.3 Cemiplimab

Cemiplimab is a monoclonal antibody that belongs to a class of drugs that binds to the PD-1 receptor, blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, with the potential for breaking of peripheral tolerance and inducing immune-mediated adverse reactions that can occur in any organ system or tissue. Immune-mediated adverse reactions reported from clinical trials with Libtayo® included: immune-mediated pneumonitis (2.4%, 62% resolution), immune-mediated colitis (0.9%, 80% resolution), immune-mediated hepatitis (2.1%, 64% resolution), immune-mediated nephritis and renal dysfunction (0.6%, 100% resolution). Immune-mediated endocrinopathies included adrenal insufficiency (0.4%), hypophysitis resulting in hypopituitarism (0.2%), hypothyroidism (6%, requiring hormone replacement), hyperthyroidism (1.5%, 38% resolution), Type 1 diabetes mellitus (0.7%). Immune-mediated dermatologic adverse reactions occurred in 1.7% (33% resolution) of patients, including erythema multiforme and pemphigoid. In addition, Stevens-Johnsons syndrome and toxic epidermal necrolysis (TEN) have also been observed as for other agent of this class. Approximately, 22% of patients had recurrence of dermatologic reactions after re-initiation of cemiplimab. Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients.

Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% or were reported with other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. Reported events by System Organ Class (SOC) included neurological (meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy), cardiovascular (myocarditis, pericarditis, vasculitis), ocular (uveitis, iritis, and other ocular inflammatory toxicities that can be associated with retinal detachment and various grades of visual impairment to include blindness can occur), gastrointestinal (pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis), musculoskeletal and connective tissue (myositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica), hematological and immunological (hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis, sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection). Systemic corticosteroids were required in almost all patients presenting with these events.

Furthermore, based on its mechanism of action, cemiplimab can cause fetal harm when administered to a pregnant woman. Conditions for eligibility of women of reproductive potential and male subjects with female partners of childbearing potential are detailed in Section 5.1.

Please refer to Libtayo® Label, SmPC and most recent IB for more detailed information.

2.3.1.4 SAR444245 combined with cemiplimab

Combining SAR444245 with cemiplimab may lead to an increased frequency and/or severity of AEs related to immune activation. Serious adverse drug reactions reported with agents known to increase immune activation include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction (see Section 2.3.1.3).

As both substances are biologic agents, they may have the propensity to induce IRRs that may have higher rate of occurrence and severity when SAR444245 and cemiplimab are used in combination.

The maximum tolerated dose of SAR444245 combined with the approved dosing of another anti-PD1 pembrolizumab is under assessment in the HAMMER study using a Q3W schedule. Safety data generated from the combination of SAR444245 and pembrolizumab have informed the selection of the combination dose in this study (See Section 4.3 for details).

2.3.2 Benefit assessment

The ability of IL-2 to expand T cells with maintenance of functional activity has been translated into the first reproducible effective human cancer immunotherapies. The first-generation IL-2 (aldesleukin) was the first immunotherapy effective for human cancer. Aldesleukin is approved in metastatic RCC and metastatic melanoma and its use has resulted in durable, complete responses in some patients with anti-tumor effects via elevations in CD8+ T cells (naïve, effector, and memory T cells). However, clinical benefit of aldesleukin requires high dose as the enhancement of the CD8+ T-cell population is mediated through the intermediate-affinity by IL-2Rβγ, the suppressor CD4+ Treg cells are preferentially enhanced at lower dose through the high-affinity IL-2Rαβγ, which is probably responsible for the limited proportion of responding patients (ORR 16% in metastatic melanoma patients - US Label), and at the price of significant toxicities.

SAR444245, as a “non-alpha” new generation IL-2 is expected to result in greater anti-tumor activity than aldesleukin that has already demonstrated clinical benefit.

Both melanoma and CSCC are tumor types that are benefiting from ICI treatment. The companion anti-PD1 cemiplimab to be combined with SAR444245 in this study is approved as 1L treatment in CSCC, an indication behaving very similarly to melanoma in its response to an ICI, and shares the same mechanism of action with two other anti-PD-1 (nivolumab and pembrolizumab) that are approved for the treatment of melanoma (see cemiplimab, pembrolizumab, and nivolumab respective labels).

In a syngeneic mouse model CT-26, relatively resistant to immune checkpoint treatment, SAR444245 potentiated the activity of an anti-PD1 antibody. Combination treatment in animals, when compared to respective monotherapies, increased the number of complete responses and prolonged survival which was durable as demonstrated by the failure of the tumor to grow upon re-engraftment on the tumor free animals, indicating the establishment of durable memory T-cell population in response to the initial treatment (see SAR444245 IB). Furthermore, preliminary clinical data from another new generation IL-2, NKTR-214, in 1L melanoma, induced increase ORR and better quality of response than historical data for anti-PD-1 treatment alone (12).

Based on cemiplimab and SAR444245 clinical and preclinical available data, the combination regimen proposed to be evaluated in this study is anticipated to bring benefit to CSCC and melanoma populations.

2.3.3 Overall benefit: risk conclusion

SAR444245, with its site-specific pegylation, was designed to substantially reduce association with the IL-2 α receptor, while retaining stimulatory activity for cells expressing the moderate affinity IL-2 βγ receptor. These design features are anticipated to minimize safety liability associated with Proleukin by avoiding expansion of immunosuppressive immune cell populations (regulatory T cells) and off-target complications such as vascular leak syndrome, while still promoting expansion of immune populations that can support anti-tumor immune responses.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with this new generation IL-2 SAR444245 combined with the anti-PD1 inhibitor cemiplimab are justified by the anticipated benefits that may be afforded to participants with melanoma or CSCC. In the 1L setting, in addition to investigational SAR444245, participants will be receiving either a standard-of-care anti-PD1 (CSCC) or an anti-PD1 with proven activity (melanoma).

2.3.4 Benefits and risks assessment in the context of COVID-19 pandemic

2.3.4.1 Risks in the context of COVID-19

2.3.4.1.1 Risks related to the patient population

Patients potentially eligible for this study have advanced or metastatic melanoma or CSCC.

Gonzalez-Cao et al. (26) have completed a national registry of melanoma patients infected by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from 01 April 2020 to 08 June 2020. Patients with a previous diagnosis of melanoma presenting with SARS-CoV-2 infection to their hospitals network, were eligible for enrollment. A prospective observational study with a case registry followed by a retrospective analysis of patient data has been performed. Sixty-four patients were included, 55% had stage IV melanoma, 33% were on active anticancer treatment with anti PD-1 antibodies. Asymptomatic/paucisymptomatic evolution of SARS-CoV-2 infection was recorded in 30% patients and for 20% patients the infection was mild in severity, with no hospital admission required. Serious and life-threatening complications were recorded in 28% and 22% patients, respectively, coronavirus disease 2019 (COVID-19) episode resolved in 55 cases, including 34 (53%) patients cured, 12% patients died due to melanoma progression and 20% patients due to COVID-19. The median age of patients who died from COVID-19 was 74 years (ranging from 49 to 91 years), while for those cured it was 64 years (ranging from 6 to 95 year). The majority of patients who died were males (85%), while this rate decreased to 62% for those cured. The mortality rate from COVID-19 was 20% for both stage IV and localized melanoma, while according to melanoma treatment it was 21%, 16%, and 21% for immunotherapy, BRAF plus MEK inhibitors, and for those who were not undergoing active cancer treatment, respectively. The authors concluded that the risk of death from COVID-19 in

melanoma patients was higher in males and older patients, which is similar to what is observed in the general population, and that the risk was not associated with neither the stage of the disease nor its therapy.

Another study (27) evaluated the impact of COVID-19 pandemic on the management of metastatic melanoma patients treated with immune checkpoint inhibitors. Of the 80 patients included in the trial (62 nivolumab and 18 pembrolizumab), a total of 57 patients maintained their treatment without interruptions, while 16 postponed it for one or two cycles. Therapy was then resumed in 10 of the 16 patients (62.5%) delayed. The remaining 7 patients suspended treatment due to progression, completion of schedule, or were lost to follow-up. None of the patients under immune checkpoint inhibitors developed SARS-CoV-2 infection. Findings from this study support the possibility of continuing ICI in metastatic melanoma patients, evaluating on a patient basis (elderly, comorbidities, ongoing response, adjuvant treatment) the possibility of delaying the subsequent course.

There are no evidence-based guidelines for the management of melanoma in the era of COVID-19. However, several guidelines designed to help making clinical decisions have been published. These include the United Kingdom (UK)-based consensus (28), the ESMO Guidelines (29), and the National Comprehensive Cancer Network recommendation (30). In the UK-based consensus guidelines, the authors have recommended PD-1 inhibitors monotherapy for patients starting immunologic therapy, while combination immunotherapy has been considered still suitable for patients with higher-risk disease.

There is no information on the risks associated with COVID-19 and advanced or metastatic CSCC, however, this cancer occurs in two important categories that are known to impact the prognosis of COVID-19 in the general population and also in melanoma: male and older populations.

Testing for SARS-CoV-2 infection during the screening phase should be at Investigator's discretion and should also follow local/international guidelines (eg, asymptomatic but high risk of infection patients, patients with symptoms that could be associated with SARS-CoV-2 infection). Patients known to have had SARS-CoV-2 infection prior to study entry must be fully clinically recovered in order to be eligible for participation in the study.

During the study, if a participant is diagnosed with SARS-CoV-2, dose modification of study intervention should be based on the recommendations provided in Section 6.6. In addition, all Investigators are instructed to consult official COVID-19 clinical research guidance from their local hospital/institution along with other relevant resources, such as:

- American society of clinical oncology (ASCO) (31),
- European Society for Medical Oncology (ESMO) (32).

2.3.4.1.2 Risks related to study treatment

The treatment regimen under evaluation in the study includes the anti-PD1 cemiplimab and the non-alpha IL-2 SAR444245.

Data from a small registry cohort showed that immunotherapy was not associated with a poor outcome of COVID-19 in melanoma patients (26) and the UK-based consensus guidelines for the management of melanoma during the COVID-19 pandemic recommends PD-1 inhibitor monotherapy for patients starting immunologic therapy, combination immunotherapy being considered still suitable for patients with higher-risk disease (28).

SAR444245 has the potential to induce CRS which could exacerbate the manifestations of COVID-19 infection. It is however worth noting that the pegylated IL-2 bempegaldesleukin is currently being evaluated for the treatment of patients with mild COVID-19 in a Phase 1b study (NCT04646044).

2.3.4.1.3 Risks related to study related activity

It is important to minimize the risk of exposure of patients to COVID-19. In addition to the contingency measures described in Section 10.13, the following prevention and mitigation plans could be implemented at clinical sites:

- All participating sites should have implemented measures according to regional/local Health Authorities, European Medicines Agency (EMA), ESMO, ASCO guidelines including but not limited to restrictions of access to the hospitals for visitors, physical distancing and personal protective equipment (PPE).
- Study participants should be treated in a dedicated area that is separated from patients with COVID-19 infection.

2.3.4.1.4 Conclusion on the benefit-risk pertaining to COVID-19

Overall, benefit-risk is deemed acceptable in patients with advanced and metastatic melanoma and CSCC during COVID-19 pandemic. Sponsor will continue to evaluate benefit-risk during the study period.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with cemiplimab.	• **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 (1). • **Cohort B** (CSCC): ORR defined as the proportion of participants who have a confirmed CR or PR determined by Investigator per RECIST 1.1, or modified WHO criteria for medical photographs of external skin lesions, or composite criteria.
Secondary	
• To determine the RP2D and to assess the safety profile of SAR444245 when combined with cemiplimab	• Incidence of TEAEs, DLTs, SAEs, laboratory abnormalities according to NCI CTCAE v 5.0 and ASTCT consensus gradings (2)
• To assess active concentrations of cemiplimab when given in combination with SAR444245	• C_{trough} and $C_{end\_of\_Infusion}$ of cemiplimab
• To assess other indicators of antitumor activity	• Complete Response rate 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 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 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 RECIST1.1 or modified WHO criteria or composite criteria, whichever relevant. • Duration of Response 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 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 including confirmed CR or PR at any time or SD 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, 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.
• To assess the concentrations of SAR444245 when given in combination with cemiplimab.	• Concentration of SAR444245
• To assess the immunogenicity of SAR444245	• Incidence of ADAs against SAR444245

Objectives	Endpoints
Exploratory	
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in an oncology study setting.

In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1/2, multi-cohort, un-controlled, 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.

SAR444245 and cemiplimab will be administered every 3 weeks in 21-day cycles.

The study includes 2 treatment cohorts:

Cohort A will include approximately 40 participants with previously untreated **locally advanced, unresectable or metastatic melanoma,** and will assess the investigational combination regimen as 1L therapy.

Cohort B will include approximately 40 participants with ICI-naïve **metastatic CSCC or locally advanced CSCC** who are not candidates for curative surgery or curative radiation and who have received no more than 2 prior lines of systemic therapy.

The study will start with a dose escalation to determine the RP2D of SAR444245 when combined with cemiplimab. The starting dose will be 16 µg/kg Q3W (DL1) with a possibility to de-escalate to 8 µg/kg Q3W (DL -1) or escalate to 24 µg/kg Q3W (DL2) based on the occurrence of DLT and overall assessment of safety. The plan is to treat a minimum number of 3 DLT evaluable participants at each dose-cohort and a minimum of 6 DLT-evaluable participants treated at RP2D will be needed before starting the dose expansion. During the dose escalation, decision for next dose level (de-escalate, stay, escalate) will occur after the last patient has completed the DLT observation period (first 21 days) for the previous dose level. The Study Board (SB) will review DLT and overall safety data for these participants and will make the next dose recommendation. DLT-evaluable participants include all participants in the dose escalation who have been treated and observed for at least 21 days. Any participant who experienced a DLT during the first 21 days will also be DLT-evaluable. The determination of RP2D will be made by the SB after a minimum of 6 DLT-evaluable participants have been treated at this selected dose. Participants enrolled in the dose escalation and treated at the RP2D will be included in the total number of participants.

The DLT observation period is 21 days and will take into account the occurrence of DLT. The Modified Toxicity Probability Interval 2 (mTPI2) design will be used in the dose escalation part. The mTPI2 design is a Bayesian interval design that can be implemented in a simple fashion as the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics. The target toxicity rate for the Maximum Tolerated Dose (MTD) is 0.3, with the acceptable toxicity probability interval of (0.25,0.35). The dose decision (stay at current dose, increase the dose or reduce the dose) will be made by the SB and will be guided by the decision rules from the mTPI2 design. The mTPI2 decision rules are based on calculating the unit probability mass (UPM) of intervals as follows: (0, 0.05), (0.05, 0.15), (0.15, 0.25), (0.25, 0.35), (0.35, 0.45) (0.85, 0.95), (0.95, 1). In the mTPI2 method, intervals that are lower than 0.25 indicate dose

escalation, equivalence interval (0.25,0.35) indicates staying at the current dose level, and intervals that are higher than 0.35 indicate dose de-escalation. The interval with the largest UPM is the winning interval and implies the corresponding dose escalation/de-escalation decision. For the dose escalation part of the study, mTPI2 rules (see Table 2) will be applied, unless decided otherwise by the SB.

Table 2 - Dose escalation rule of the modified toxicity probability interval-2 method

		Number of DLT-evaluable participants									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Number of dose limiting toxicities	**0**	E	E	E	E	E	E	E	E	E	E
	1	D	D	S	S	E	E	E	E	E	E
	2		DU	D	D	D	S	S	S	E	E
	3			DU	DU	D	D	D	D	S	S
	4				DU	DU	DU	D	D	D	D
	5					DU	DU	DU	DU	DU	D
	6						DU	DU	DU	DU	DU
	7							DU	DU	DU	DU
	8								DU	DU	DU
	9									DU	DU
	10										DU

E: Escalate to the next higher dose, S: Stay at the current dose, D: De-escalate to the next lower dose, DU: De-escalate to the next lower dose and the current dose will never be used again because unacceptable high toxicity.

Dose limiting toxicity: The following events occurring during the DLT observation period (21 days of first cycle) are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245.

Hematologic abnormalities:

- Any Grade 4 neutropenia irrespective of duration
- Any febrile neutropenia
- Grade 3 thrombocytopenia associated with transfusion in addition to bleeding and any Grade 4 thrombocytopenia

Non-hematologic abnormalities:

- Grade 3 or above ALT and AST increase
- Grade 3 or above Vascular Leak Syndrome (VLS)
- Grade 3 or above hypotension
- Grade 3 or above cytokine release syndrome
- Grade 3 or above AE that does not resolve to grade ≤2 within 7 days of starting accepted standard of care medical management
- Grade 4 laboratory abnormalities

Study Board

The study Investigators (or designee) participating in the dose escalation part of the trial and the Sponsor clinical team members will constitute the Study Board (SB). The SB will meet first when the first patient is treated in the dose escalation part and will review clinical data of each individual patient treated in the dose escalation part on a regular basis, in order to adjust the number of patients to be enrolled and to decide dose confirmation, dose reduction, dose escalation as appropriate on the basis of their knowledge of the safety data. Minutes of each meeting will be written by the Sponsor and distributed to all sites participating in the dose escalation. Decisions regarding final dose selection will be made during one of the study board meeting and documented in the meeting minutes.

After dose escalation, occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants per regimen will trigger SB to rapidly convene to assess safety or need to pause enrollment to allow for a safety review. Study Board (during dose escalation), Data Monitoring Committee (DMC) (during dose expansion) and Sponsor can decide to stop any cohort in case excessive toxicity (for example but not limited to excessive ir-AE or excessive number of G4/5 events) is observed.

Special considerations pertaining to methodology

Interactive Response Technology will be used to control recruitment assignment per site and facilitate drug supply.

The duration of the study for a participant will include:

- **Screening period**: up to 28 days.
- **Treatment Period**: enrolled participants will receive continuous treatment until PD, unacceptable AE, other full permanent discontinuation criteria as described in Section 7, or completion of Cycle 35.
- **End of Treatment and Follow-up.** End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **EOT**:
    1. Participants who discontinue study treatment **without radiological or clinical PD** or who **complete 35 cycles of treatment without PD** (per RECIST 1.1 or modified WHO Criteria for medical photographs), will be followed for safety (as per Schedule of Activities [SoA]) and tumor imaging assessments every 3 months ±7 days from last IMP administration, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.
    2. Participants who discontinue study treatment **with radiological or clinical PD** (per RECIST 1.1 or modified WHO Criteria for medical photographs **or** [redacted] will be followed in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration, before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-Up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. However, updated survival status may be requested by the Sponsor at any time during the course of the study. Survival Phone Call Follow-Up will continue 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 at any prior timepoint.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that combining the immune-checkpoint inhibitor cemiplimab with the non-alpha IL-2 SAR444245 will result in a significant increase in the percentage of ICI-naïve patients with melanoma and CSCC experiencing an objective response.

Several new generation IL-2 are currently under clinical development. The most advanced compound is NKTR-214 (bempegaldesleukin), an IL-2βγ-biased cytokine that has shown therapeutic benefit when combined with nivolumab in early phase clinical trials, which brought it to earn FDA breakthrough therapy designation for advanced melanoma. The FDA's decision was based on 12-month follow-up results of the ongoing PIVOT-02 Phase 1/2 clinical trial (NCT02983045). In this subset, 63.6% of the patients showed response to treatment, including participants whose tumor were PD-L1 negative with minimal T-cell infiltration, with a complete response rate of 34% (25). It is currently in Phase 3 development in various indications including in 1L melanoma (NCT03635983). The ORR of ~64% is increased by 20% from the ORR of 44% reported for nivolumab alone in CheckMate-067 (9), as per Investigator's assessment, although translation of this effect on OS has not yet been demonstrated.

As single agent, cemiplimab has demonstrated an ORR of 47% and 44% for in ICI-naïve metastatic CSCC and locally advanced CSCC, respectively, as per independent central review, rates that are similar to that observed with other ICIs in the ICI-naïve melanoma (10, 11). We may anticipate a similar effect of the SAR444245 + cemiplimab combination in that indication.

The proposed study is a non-randomized study where the experimental combination will be assessed in a single cohort for each indication, using historical data for single agent immune-checkpoint as a benchmark to show outstanding objective response rate. The ORR will be assessed using either RECIST 1.1, and/or the modified WHO criteria for medical photographs of skin lesions, whichever the most relevant, for participants with locally advanced diseases or with metastatic disease with or without skin target lesions. The objective response will be assessed per Investigator in first intention; a central review will only be done for confirmation of compelling results. In patients with localized CSCC, the documentation of complete response will be exploratory from an optional tumor biopsy specimen.

Although cemiplimab is approved for the treatment of ICI-naïve metastatic or locally advanced CSCC, it is not approved for the treatment of patients with melanoma. However, as an anti-PD1, cemiplimab shares the same mechanism of action as nivolumab and pembrolizumab, both approved for the treatment of melanoma, and has exhibited an antitumor activity comparable to pembrolizumab in NSCLC patients with PDL-1 TPS ≥50% (33), thus justifying its investigation for both tumor types in this clinical study.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

Dose escalation for SAR444245 monotherapy and in combination with pembrolizumab or cetuximab is ongoing in the first-in-human HAMMER study. Data from a total of 68 patients who have received SAR444245 Q2W or Q3W in monotherapy, in a Q3W regimen in combination with pembrolizumab 200 mg Q3W, or with cetuximab 400/250 mg/m^2 QW is available as of 18 June 2021.

The dose levels tested to date for SAR444245 monotherapy administered using a Q3W schedule are 8 µg/kg (n=4), 16 µg/kg (n=6), 24 µg/kg (n=11), and 32 µg/kg (n=6) and 40 µg/kg (n=2).

In combination with pembrolizumab, SAR444245 has been administered Q3W at the doses of 8 µg/kg (n=4), 16 µg/kg (n=9), 24 µg/kg (n=6), 32 µg/kg (n=1). In combination with cetuximab, SAR444245 has been administered Q3W at 16 µg/kg (n=5) or 24 µg/kg (n=5).

For monotherapy cohort, the only DLT observed to date is a Grade 3 infusion-related reaction (occurred at C2D1 which resolved on the same day with supportive care) reported in a patient on 32 µg/kg Q3W monotherapy.

For SAR444245 in combination with pembrolizumab 200 mg Q3W, 1 DLT (Grade 3 liver enzyme elevation with Grade 2 bilirubin elevation meeting drug-induced liver injury [DILI] criteria occurred in C1D1 which resolved after 7 days with steroids) was observed in a participant with SAR444245 24 µg/kg Q3W with pembrolizumab.

No DLTs were reported by SAR444245 cetuximab combination cohort (SAR444245 24 µg/kg Q3W).

Grade 3/4 TEAEs commonly reported by participants who received SAR444245 24 µg/kg monotherapy (n=11) include in particular Grade 4 lymphocyte count decreased/lymphopenia (7 participants, 63.6%), Grade 3 anemia (3 participants, 27.3%), and Grade 3 dyspnea (2 participants, 18.2%). Of note, transient lymphocyte count decrease in the peripheral blood is an expected effect, consequence of T cell activation and temporary compartmental redistribution after IL-2 treatment. Nevertheless, this phenomenon can be reported as an adverse event (AE) in HAMMER study.

Grade 3/4 TEAEs reported by participants who received SAR444245 24 µg/kg in combination with pembrolizumab (n=6) include Grade 4 lymphocyte count decreased (3 participants, 50.0%), Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT) & gamma-glutamyl transferase (GGT) increased (2 participants each for AST & ALT increased, 33.3%; 1 participant for GGT increased, 16.7%), Grade 3 blood phosphorus decreased & hypophosphatemia (1 participant each, 16.7%), and Grade 3 dyspnea (1 participant, 16.7%).

Grade 3/4 TEAEs reported by participants who received SAR444245 24 µg/kg in combination with cetuximab (n=5) include Grade 3 chills (1 participant, 20.0%) and Grade 3 abdominal pain and vomiting (1 participant for each, 20.0%).

Within the HAMMER study, all together there were 13 patients that experienced any grade of CRS (per CTCAE version 5). Only 1 Grade 4 CRS with Grade 3 hypertension, Grade 2 fever, and Grade 2/3 neurological symptoms (with 24 µg/kg Q3W, 2.6%) is reported among participants who received SAR444245 monotherapy (n=38). From participants who received SAR444245 pembrolizumab combination (n=20), Grade 3 CRS (with 16 µg/kg Q3W) is observed in 1 participant (5.0%) with Grade 3 hypotension and Grade 2 fever.

According to literature, prophylactic hydration on the dosing days could mitigate incidence and severity of hypotension as part of CRS. As HAMMER study was not mandating prophylactic hydration before January 2021, the participants who experienced CRS in HAMMER study did not always receive peri-infusion hydration. Based on this learning, hydration and CRS management guidelines have been included in the Phase 2 study protocols.

With respect to PK, SAR444245 exposure increased in an approximately dose-proportional manner in the monotherapy cohorts, and no impact of anti-drug antibody (ADA) on SAR444245 PK could be identified. Also, in the combination cohort, there was no apparent impact of pembrolizumab on the PK of SAR444245.

Differently from native IL-2 and aldesleukin, SAR444245 does not have high potency at the IL-2Rα/β/γ receptor subunit expressed on T regulatory (Treg) cells because the site-specific pegylation blocks IL-2Rα engagement and demonstrates high potency at the IL2Rβ/γ receptor subunit expressed on CD8+ T and natural killer cells (NK). Due to this re-programmed receptor bias, SAR444245 induces proliferation of peripheral CD8+ T and NK cells and less impact on immunosuppressive Treg cells. Therefore, we closely monitored the PDy change of CD8+ T, NK and Treg cells in HAMMER study as supportive information for R2PD selection.

In the SAR444245 monotherapy dose levels (8 µg/kg, 16 µg/kg and 24 µg/kg and 32 µg/kg Q3W), the PDy data suggest that a trend for dose-dependent expansion of CD8+ T cells and NK cells has been achieved. In the 8 µg/kg dose levels, the average increase in peripheral blood CD8+ T cells over baseline at 72 hours post dose was 1.75-fold. For dose levels 16 µg/kg and 24 µg/kg, the peripheral blood CD8+ T cell expansion was 2.47 and 4.47-fold at the Day 8 postdose peak of expansion. The Day 8 sample timepoint was added after the first 3 participants in the 8 µg/kg cohort were dosed.

In addition, the average increase in peripheral blood NK cells was 4.22-fold at 72 hours for 8 µg/kg. The 16 µg/kg and 24 µg/kg dose levels resulted in 5.9 and 7.67-fold NK expansion, compared to baseline at the Day 8 peak expansion. Among the dose levels tested to date for SAR444245 in combination with pembrolizumab administered using Q3W schedule, we have collected available PDy data for the 8 µg/kg (n=4) and 16 µg/kg cohort (n=6), in which the average increase in CD8+ T cells, compared to baseline, is 2.06-fold and 3.71-fold, respectively; and the average increase in NK cells, compared to baseline, is 6.73-fold and 13.43-fold, respectively at the peak expansion Day 8. In addition, the comparison of T and NK cell expansion between [redacted] µg/kg and [redacted] µg/kg cohorts indicated that the anticipated maximum CD8+ T and NK cells expansion PDy effect may have been achieved at[redacted] µg/kg cohort. Based on these data, additional quantitative systems pharmacology (QSP) and population PK/PDy models were developed and indicated that the increase of CD8+ T and NK cells was less than proportional with increasing dose, suggesting a flattening of the dose-response curve.

In addition, preclinical studies using human whole blood to assess the induction of cytokines showed no change in cytokine profiles when administering SAR444245 with and without pembrolizumab. This study used SAR444245 concentration ranges that went significantly higher than current clinical dosages (0.2-4.5 µg/mL) and showed that SAR444245-induced cytokine release in human whole blood was not affected in the presence of pembrolizumab at Q3W schedule.

Considering that: SAR444245 monotherapy up to 32 µg/kg Q3W and pembrolizumab combination up to 32 µg/kg Q3W are cleared in HAMMER study; sustained relevant PDy effect in blood was documented in all patients tested to date; the Sponsor does not anticipate early overlapping toxicities when combined with an approved dose of an anti-PD1, as suggested by the tolerability reported in the patient cohort receiving SAR444245 at the 16 µg/kg Q3W dose in combination with the pembrolizumab 200 mg dose.

As the safety profile of anti-PD-1 is generally overlapping a dose escalation will be conducted starting at 16 µg/kg Q3W with a potential option to de-escalation to 8 µg/kg Q3W or escalate to 24 µg/kg Q3W based on the occurrence of DLT and overall assessment of safety. The minimum number of DLT evaluable participants will be 3 at each dose decision and a minimum of 6 DLT-evaluable participants treated at RP2D are needed before starting the dose expansion.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if the following criteria apply:

Age

I 01. Participant must be ≥18 years of age (or country's legal age of majority if >18 years), at the time of signing the informed consent.

Type of participant and disease characteristics

Cancer diagnosis

I 02. *For participants in Cohort A:* Participants with histologically-confirmed unresectable locally advanced or metastatic melanoma that are not amenable to local therapy, based on the Investigator's judgement at the time of potential enrollment. The eligibility of participants to take part in the study will be validated at a multidisciplinary collegial meeting in countries where it is required.
- In Ireland Cohort A will not be open to enrollment (See Appendix 7, Section 10.7)
- In France participants with BRAF-mutant melanoma will not be included in Cohort A (See Appendix 7, Section 10.7)

I 03. *For participants in Cohort B*: Participants with histologically-confirmed metastatic CSCC or locally advanced CSCC, with special considerations for the following categories:
- Participants with tumors arising on the cutaneous hairbearing (non-glabrous) lip with extension onto dry red lip (vermillion) may be eligible after communication with and approval from the Sponsor.
- Participants for whom the primary site is nose are only eligible if the Investigator is able to establish unambiguously that the primary site was skin, not nasal mucosa with outward extension to skin.
- Participants with mixed histology in which the predominant histology is invasive CSCC (with only a minimal component of mixed histology) may be eligible after communication with and approval from the Sponsor.

I 04. *For participants in Cohort B*: Participants with locally advanced CSCC who are not candidates for curative surgery.
- Surgery must be deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment must be submitted.

I 05. *For participants in Cohort B*: Participants with locally advanced CSCC who are not candidates for curative radiation.

- Participants must be deemed as not appropriate for radiation therapy, EITHER in the opinion of a radiation oncologist, with copy of the consultation note from a clinical visit within 60 days of enrollment that must be submitted, OR in the opinion of the Investigator indicating that the benefit/risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist AND EITHER a medical oncologist with expertise in cutaneous malignancies, OR a dermato-oncologist, OR a head and neck surgeon. A clinic note from the Investigator stating that this benefit/risk assessment was performed should be submitted.

I 06. Provision of tumor tissue:

- **Mandatory baseline biopsy** for participants in **Cohort A with skin metastasis and participants in Cohort B.** Archival tumor tissue sample is acceptable if obtained within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment (minimum **10 slides with 4-5 microns thickness**). **Mandatory on-treatment biopsy** for participants in **Cohort A with skin metastasis and participants in Cohort B**. O**ne biopsy on treatment** is mandatory for participants to **Cohort A** with skin metastasis, if clinically feasible. **One biopsy on treatment** is mandatory for participants in **Cohort B**, if clinically feasible.
- For participant enrolled in the dose escalation dose 16 µg/kg: Screening (baseline) tumor tissue collection is optional, but highly recommended. On-treatment tumor collection is not required
- For participant enrolled in the dose escalation dose 24 µg/kg: Screening (baseline) tumor tissue collection is mandatory. On-treatment tumor collection is optional but highly recommended.
- Depending on the number of acquisitions of on-treatment tumor biopsies, a participant who does not agree to on-treatment biopsy or agrees to only one on-treatment biopsy may still be eligible after discussion with the Sponsor. On-treatment biopsies should be preferably sampled from same site as baseline/archival tumor. Slide specifications are detailed in Lab Manual.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - location of the tumor not amenable to biopsy due to significant risk, OR
  - less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment
- **Optional** for participants in **Cohort A without skin metastasis**.
- Tumor site used for biopsy must not have been irradiated previously and must not be the only measurable lesion.

I 07. Measurable disease:

- *For participants in Cohort A:* At least one measurable lesion per RECIST 1.1 criteria.
- *For participants in Cohort B*: 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.

Sex

I 08. All (male and female)

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

- Male participants are eligible to participate if they agree to the following during the intervention period and for at least 210 days (corresponding to time needed to eliminate study intervention(s) plus an additional 90 days [a spermatogenesis cycle]) after the last dose of study intervention:
  - Refrain from donating or cryopreserving sperm

  PLUS either**:**
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent OR
  - Must agree to use contraception/barrier as detailed below:
    - A male condom with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant, or during homosexual intercourse

b) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

  OR
  - Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 (Section 10.4) during the intervention period (to be effective before starting the intervention) and for at least 180 days [corresponding to the time needed to eliminate any study intervention(s) plus 30 days (a menstrual cycle)] after the last dose of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
  - A WOCBP must have a negative highly sensitive pregnancy test (as required by local regulations) within 7 days before the first dose of study intervention
  - Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4 (Section 10.4).
  - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 09. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Cancer diagnosis

E 01. *For participants in Cohort A:* Participants with uveal or ocular or desmoplastic melanoma.

E 02. *For participants in Cohort B:* Participants for whom the primary site of CSCC was the dry red lip (vermillion) or the anogenital area (vulva, penis, scrotum, and perianal region).

E 03. *For participants in Cohort B:* Participants with mixed CSCC histologies (eg, sarcomatoid, adenosquamous).

Medical conditions

E 04. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2.

E 05. Predicted life expectancy ≤3 months.

E 06. Active brain metastases or leptomeningeal metastases;
- Patients with previously treated brain metastases are eligible provided they are clinically stable for at least 4 weeks with no evidence of new or enlarging brain metastases and have not received corticosteroids 2 weeks prior to first IMP administration (Note: participants with brain involvement due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval from the Sponsor).
- Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) are eligible but will require regular imaging of the brain as a site of disease.

E 07. History of allogenic tissue/solid organ transplant (participants with prior corneal transplant may be allowed to enroll after discussion with and approval from Sponsor).

E 08. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 agents and anti-cytotoxic T-lymphocyte associated protein 4 monoclonal antibodies) that caused permanent discontinuation of the agent, or that were Grade 4 in severity.

E 09. Last administration of prior antitumor therapy (chemotherapy, targeted agents, and immunotherapy) or any investigational treatment within 28 days or less than 5 times the half-life, whichever is shorter; major surgery or local intervention within 28 days.

E 10. History of pneumonitis within the last 5 years, active pneumonitis, interstitial lung disease requiring the use of steroids, idiopathic pulmonary fibrosis, confirmed pleural effusion, severe dyspnea at rest or requiring supplementary oxygen therapy.

E 11. Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 2 weeks of IMP initiation. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder. Participants who require a brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.

E 12. Antibiotic use (excluding topical antibiotics) ≤14 days prior to first dose of IMP, or any serious systemic fungal, bacterial, viral (excluding viral infection settings as described in E 17), or other infection that is not controlled or requires IV or oral antibiotics.

E 13. Severe or unstable cardiac condition within 6 months prior to starting study treatment, such as congestive heart failure (New York Heart Association Class III or IV), cardiac bypass surgery or coronary artery stent placement, angioplasty, left ventricular ejection fraction (LVEF) below 50%, unstable angina, medically uncontrolled hypertension (eg, ≥160 mmHg systolic or ≥100 mmHg diastolic), uncontrolled cardiac arrhythmia requiring medication (≥Grade 2, according to NCI-CTCAE v 5.0), or myocardial infarction.

E 14. Ongoing AEs caused by any prior anti-cancer therapy ≥Grade 2 (NCI-CTCAE v 5.0). Participants with ≤Grade 1 peripheral neuropathy, or Grade 2 alopecia, are permitted.

E 15. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). The following are not exclusionary: vitiligo, childhood asthma that has resolved, psoriasis that does not require systemic treatment.

E 16. Receipt of a live-virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 17. HIV infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease or known uncontrolled infection with human immunodeficiency virus (HIV). HIV infected participants must be on anti-retroviral therapy (ART) and have a well-controlled HIV infection/disease defined as:

- Participants on ART must have a CD4+ T-cell count >350 cells/mm^3 at time of screening
- Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening
- Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1)
- Combination ART regimen must not contain any antiretroviral medications other than: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, or tenoforvir.

E 18. Known uncontrolled hepatitis B infection, known untreated current hepatitis C infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment.
- To control HBV infection, participants with positive HBsAg should have started anti-HBV therapy before initiation of IMP. Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.
- Participants who are positive for anti-hepatitis B core antibody HBc, negative for hepatitis B surface antigen (HBsAg), and negative or positive for anti-hepatitis B surface antibody (HBs), and who have an HBV viral load under 100 IU/mL, do not require HBV anti-viral prophylaxis.
- Participants with past or ongoing HCV infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month prior to starting study intervention. Participants with positive HCV antibody and undetectable HCV RNA without anti-HCV therapy are eligible.

E 19. Known second malignancy either progressing or requiring active treatment within the last 3 years, except for tumors with negligible risk of metastasis or death, such as adequately treated basal cell carcinoma of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or history of prostate adenocarcinoma treated with curative intent at least 3 years ago, and with undetectable prostate-specific antigen for at least 3 years prior to enrollment.

E 20. Known hypersensitivity to or contraindication for the use of any study intervention or components thereof including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein.

E 21. Participants with baseline SpO2 ≤92% (without oxygen therapy).

Prior/concomitant therapy

E 22. Has received prior IL-2 based anti-cancer treatment.

E 23. Is unable or unwilling to take premedication.

E 24. Deleted in Amended protocol 04

E 25. *For participants in Cohort A*: Participants who have received any systemic treatment for their advanced/metastatic disease.

E 26. *For participants in Cohort B*: Participants who have received more than 2 prior lines of any systemic treatment for their advanced/metastatic disease.

E 27. *For participants in Cohort A and Cohort B*: Participants who have received approved or investigational anti-PD1, anti-PD-L1, or anti-PD-L2 or anti-CTLA4 (or any other antibody or drug specifically targeting T-cell co-stimulation) except in the context of adjuvant or neoadjuvant. Participants who joined a study with an investigational anti-PD-1/PD-L1 but have written confirmation they were on control arm are allowed.

E 28. *For participants in Cohort A and Cohort B*: Participants who have received adjuvant or neoadjuvant therapy during the 6 months prior to development of metastatic disease.

E 29. *For participants in Cohort B*: Any anticancer treatment (chemotherapy, targeted systemic therapy, radiation therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of IMP or planned to occur during the study period (participants receiving bisphosphonates or denosumab are not excluded). Notes: For participants with multiple CSCCs at baseline that are not designated by the Investigator as target lesions, treatment of these non-target CSCCs with surgery may be permitted but must be discussed with the Sponsor prior to any surgical procedure.

E 30. Participants treated under anti-hypertensive treatment who cannot temporarily (for at least 36 hours) withhold antihypertensive medications prior to each IMP dosing.

Prior/concurrent clinical study experience

E 31. Participation in a concurrent clinical study in the treatment period.

Organ and bone marrow function

E 32. Absolute neutrophil count <1500/µL (1.5×10^9/L) (after at least one week off G-CSF).

E 33. Platelets <100 × 10^3/µL (after at least 3 days without platelet transfusion).

E 34. Hemoglobin <9 g/dL (without packed red blood cell [pRBC] transfusion within prior 2 weeks). Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

E 35. Total bilirubin >1.5 x upper limit of normal (ULN) unless direct bilirubin ≤ULN (Participants with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)

E 36. Aspartate aminotransferase and alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases).

E 37. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² (Modification of Diet in Renal Disease [MDRD] Formula).

E 38. International Normalized Ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT]) >1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

Diagnostic assessments

E 39. Inability to undergo any contrast-enhanced radiologic response assessment with the following precision and exception:

- A participant who is unable to undergo computed tomography (CT) with iodinated contrast (eg, due to contrast allergy) would not be excluded if his/her disease can be

measured by magnetic resonance imaging (MRI) with gadolinium. A participant who is unable to undergo MRI with gadolinium would not be excluded if his/her disease can be measured by CT scan with contrast.

- A participant with CSCC who is unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may be eligible if the participant's disease can be comprehensively assessed with digital medical photography, after communication and approval from the Sponsor.

Other exclusions

E 40. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 41. Any country-related specific regulation that would prevent the participant from entering the study (see Section 10.7).

E 42. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 43. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 44. Any specific situation during study implementation/course that may raise ethics considerations.

E 45. History or current evidence of any condition, therapy that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No food or drink restrictions are required. Guidelines on fluid intake are presented in Section 6.1.3.

5.3.2 Caffeine, alcohol, and tobacco

No restrictions are required.

5.3.3 Activity

Participants are advised to abstain from strenuous exercise and avoid long hot showers and saunas on Days 1 to 4 of every treatment cycle.

5.3.4 Hydration

Since SAR444245 may induce episodes of hypotension participants should be informed of the importance of being well hydrated and provided hydration instructions. Guidelines pertaining to fluid intake on the day of SAR444245 dosing and for the 3 days after administration are detailed in Section 6.1.3.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure reason may not be expected within a reasonable time frame, will be recorded as screen failures. In case the participant is a temporary screen failure (ie prolonged screening), there is no need to have participant re-consent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered to the additional pages.

A participant who screen failed may be rescreened; in this situation, the rescreened participant should sign a new ICF. A participant may be rescreened only once.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING/ENROLLMENT/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 10.13.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

In both Cohort A and Cohort B, study interventions will be administered according to the following sequence: [redacted].

Participants will receive study treatment until confirmed PD, unacceptable toxicity, other full permanent discontinuation criteria as described in Section 7, or completion of Cycle 35. Beyond 35 cycles and outside of the frame of this clinical study, the Investigator may decide to pursue treatment with the anti-cancer treatment of his choice.

6.1.1 Investigational medicinal product

Investigational medicinal product is defined as SAR444245 + cemiplimab combination. Details of each IMP component to be administered are shown in Table 3. Preparation and administration of IMP are detailed in the pharmacy manual.

Hydration is required before and after SAR444245 infusion. Details are provided in Section 6.1.3.

Table 3 - Overview of IMP administered

Intervention name	SAR444245	cemiplimab
Type	Biologic	Biologic
Dose formulation	Concentrate for solution for infusion	Concentrate for solution for infusion
Unit dose strength(s)	2 mg/mL	350 mg/7 mL
Dosage level(s)[a]	Dose escalation: 16 µg/kg (DL1), 8 µg/kg (DL-1), 24 µg/kg (DL2) every 3 weeks. Dose expansion: RP2D (recommended by SB)	350 mg every 3 weeks
Route of administration	IV infusion over 30 minutes [redacted]	IV infusion over 30 minutes through an IV line containing a sterile 0.2 micron to 5 micron in-line or add-on filter
Use	experimental	experimental
Packaging and labeling	Supplied in a single-dose vial in a treatment box. Each vial contains 2 mg/mL and has an extractable volume of 1 mL. Each vial and treatment box will be labeled as required per country requirement.	Supplied in a single-dose vial in a treatment box. Each vial contains 350 mg/7 mL (50 mg/mL). Each vial and treatment box will be labeled as required per country requirement.
Current names or aliases	Not applicable	Libtayo®

a The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, the participant must still be weighed on D1 of each cycle, and the weight recorded in the eCRF.

6.1.2 Non-investigational medicinal product

6.1.2.1 Premedication for SAR444245

All participants will receive the following premedication to prevent or reduce the acute effect of infusion-related reactions (IRRs) or flu-like symptoms, approximately 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 (or equivalent), and then optionally thereafter as needed.
- Diphenhydramine 25 to 50 mg IV or oral route (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 be optional after 4 cycles in the below scenarios:

- For a participant who has no IRR for the first 4 cycles premedication for the subsequent infusions is optional at the Investigator's discretion (based on participant medical history, disease characteristics and other TEAEs, for example but not limited to CRS, flu-like symptoms observed until Cycle 4, part or all premedication components may be omitted). However, if during the subsequent infusions without premedication the participant experiences an IRR (any grade or other TEAEs that could be mitigated by any components of premedication), premedication must be restarted for all subsequent infusions.
- If a participant develops an IRR Grade <2 during their first cycle only and then experiences no further IRRs during their next 3 cycles the Investigator may consider omitting premedication for the next cycle. If no IRR is observed for the next cycle without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion (based on participant medical history, disease characteristics and other TEAEs, for example but not limited to CRS, flu-like symptoms observed until Cycle 4, part or all premedication components may be omitted). However, if during the next cycle without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent cycles.

6.1.3 Hydration guidelines for SAR444245 administration

[redacted]

6.1.4 Readiness for treatment of severe cytokine release syndrome

Doses of tocilizumab should be available at site at all time in the event that a participant requires rapid intervention for the treatment of severe CRS. Please refer to Section 6.6.4.3 for detailed guidelines for the management of CRS.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

Treatment preparation and administration (including compatible materials) will be further detailed in the pharmacy manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Participants must be dosed at the site and will receive IMP directly from the Investigator or designee, under medical supervision. The person responsible for drug dispensing is required to maintain adequate records of the IMP administration. These records include the date the IMP components are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number and the treatment number on the vial must be recorded on the drug accountability form. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (e-CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on trial therapy schedule requires the mutual agreement of the Investigator, the Sponsor and the participant.

6.5.1 Acceptable concomitant medications

All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (e-CRF) including all prescription OTC, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of route, and date will also be included on the e-CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed, after discussion with and approval by the Sponsor.

All concomitant medications received within 30 days before the first dose of trial treatment through the Follow-up Visit should be recorded.

Colony-Stimulating Factors

Routine use of colony-stimulating factors (CSFs) is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed (34).

6.5.2 Prohibited concomitant medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment period of this trial:

- Antineoplastic systemic chemotherapy (including chemotherapies and targeted therapies) or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Investigational agents other than specified in this protocol.
- Radiation therapy for tumor control (please refer to Section 6.5.1 for allowed radiotherapy).

- Live vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, seasonal flu (seasonal flu vaccines that do not contain live virus are permitted), nasal H1N1 flu, rabies, Bacillus Calmette–Guérin (BCG), and typhoid.
- Systemic glucocorticoids and other immunosuppressive therapies such as anti-TNF, anti-IL6, etc, except for:
  - Treatment of immune-mediated AEs when indicated (IRR, CRS, irAE, and ICANS, see Table 4, Table 5, Table 6, and Table 7),
  - Treatment of any life-threatening emergency,
  - Physiologic replacement as long as they are not being administered for immunosuppressive intent, and
  - A brief course (≤7 days) of systemic corticosteroid for prophylaxis (eg, contrast dye allergy) or for the treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reactions caused by contact allergen).

Participants who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the Observation and Survival Follow-up Period.

For withholding antihypertensive medications as part of hydration guidelines, please refer to Section 6.1.3.

6.6 DOSE MODIFICATION

6.6.1 General rules

Dose modifications for SAR444245 (reduction) are permitted according to the guidelines described in this section. No dose modification is recommended for cemiplimab. Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor, unless required for immediate participant safety.

Cycle delay (ie, delay of both IMP components) is permitted in case of TEAE. Dose modification will be made according to the worst grade of toxicity observed within a cycle. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative recommended dose adjustment should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other TEAE that, in the opinion of the Investigator, warrants discontinuation.

If any of the IMP components is permanently discontinued, the other IMP component can be continued until disease progression or other criteria as detailed in Section 7.1.1 are met. In this case it is **partial permanent discontinuation** and the end of treatment (EOT) assessment will be 30 days after the date of the last administration of the remaining IMP. When both IMP components are permanently discontinued it is **full permanent discontinuation**.

All changes to study treatment administration must be recorded in the e-CRF.

6.6.2 Cycle delay

The treatment window is ±3 days for each of the Q3W administrations. A cycle is deemed to have been delayed if the treatment is administered ≥4 days beyond the theoretical day of Q3W IMP administration. The participant may receive all IMP components once the toxicity resolves or improves to Grade 1 or baseline, as described in Section 6.6.3.

Participants may have cycle delay if toxicity occurs and the participant does not recover according to following rules:

- For Q3W IMP administration: If toxicity occurs and the participant does not recover on the day of planned administration, the cycle will be delayed; restart of study IMPs could occur only on the initiation of the subsequent cycle.
- In case of cycle delay for the recovery of toxicity, the following rules should be followed for restart or discontinuation of the treatment:
  - In case of a cycle delay up to 14 days, it is per Investigator's decision to restart the study treatment.
  - After a cycle delay of >14 days and ≤84 days, it is per Investigator's decision to restart the study treatment, if a clear benefit from treatment is observed and after consultation with the Sponsor.
  - The study treatment must be permanently discontinued if the cycle delay is longer than 84 days.
- Cycle may be delayed for situations other than TEAEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days of the scheduled interruption, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for this delay should be documented in the participant's study record.

6.6.3 General guidelines for the management of treatment-related adverse events

Participants who experience Grade ≥3 treatment-related adverse events (TRAEs) at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1) will be required to temporarily withhold the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After treatment withhold, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline. Treatment resumption is at the discretion of the Investigator and

Sponsor, if thought to be in the best interest of the participant, except when specified otherwise in this protocol, or if the event has required the IMP temporary interruption for more than 84 days from the last scheduled dose.

The withholding of treatment for Grade 2 events is left at the discretion of the Investigator unless otherwise specified in this protocol.

No withholding of treatment or dose modification is required for Grade 1 events.

No dose reduction is recommended for cemiplimab. Dose reduction for SAR444245 during the dose escalation may be decided when specified in the protocol or following discussions with the Sponsor.

The final decision on dose modification and/or corrective therapy will be based on the Investigator's judgment, in the best interest of the participant.

Study intervention should be held in case of significant cardiac event (if possible, confirmed by a cardiologist) or suspicion of an immune-mediated myocarditis until it has been assessed for a relationship to SAR444245 or cemiplimab.

Recommended guidelines for the management of specific adverse events including irAE, CRS, VLS and IRR are presented in Section 6.6.4.

6.6.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as AESIs, depending on grading according to NCI-CTCAE v 5.0 (see Section 8.3.8). In case a specific adverse event meets the AESI definition it must be documented in the e-CRF.

6.6.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1, prior to SAR444245 administration, to prevent or reduce the incidence or severity of IRRs.

An infusion-related reaction in this study is defined as any signs or symptoms which develop during the infusion or up to 24 hours after the completion of the infusion. The term IRR indicates only a specific temporal relationship with the infusion and does not specify a particular mechanism underlying the signs or symptoms.

Guidelines for the management of IRR events are provided in Table 4. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing instructions, please see Section 6.1.2.1.

Table 4 - Guidelines for the management of infusion-related reactions

Event severity (NCI-CTCAE v 5.0)	Recommended IMP dose modification and Supportive care guidelines
Grade 1: Infusion interruption or intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] or cemiplimab[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 or cemiplimab infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE v.5.0 definition. If IRR happens after completion of infusion, increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.
Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours)	Interrupt SAR444245 or cemiplimab infusion. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the participant will be premedicated according to Section 6.1.2.1 for the next scheduled dose. Give the next infusion at half the infusion rate. During or after completion of infusion, additional appropriate medical therapy may include but not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics. Increase monitoring of vital signs will be as medically indicated until the participant recovers.
Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: Life-threatening; urgent intervention indicated	For both Grade 3 and Grade 4 IRRs: If IRR is clearly attributable to SAR444245 infusion, permanently discontinue SAR444245. The participant can continue treatment with cemiplimab. If IRR occurs during cemiplimab infusion, permanently discontinue both SAR444245 and cemiplimab. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

a Information for preparation and storage of SAR444245 and cemiplimab are provided in the pharmacy manual.
b In cases of anaphylaxis, epinephrine should be used immediately
Abbreviations: CTCAE=common terminology criteria for adverse events; IRR=infusion-related reaction; IV=intravenous; NCI=National Cancer Institute; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.6.4.2 Anaphylaxis

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of both SAR444245 and cemiplimab.

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased

monitoring of vital signs as medically indicated, until the participant recovers (see guidelines in 35, 36, 37).

6.6.4.3 Fever, flu-like symptoms, and cytokine-release syndrome (CRS)

Fever can frequently happen with infusion of IL-2 and may possibly evolve into flu-like symptoms or could be an early manifestation of CRS.

Fever or flu-like symptoms should be graded according to CTCAE v 5.0 and managed according to institutional standards.

Cytokine release syndrome should be graded as per ASTCT criteria integrated with central laboratory cytokine results and managed per guidelines in Table 5. If any grade of CRS is suspected, sites should make every effort to draw an additional blood sample for cytokines levels (by central laboratory) prior to the administration of tocilizumab, as well as CRP and ferritin (by local laboratory).

Sites should have at least 2 full doses of tocilizumab available and access to an intensive care unit (ICU), in case participants develop CRS.

Guidelines for management of CRS events according to severity grading are provided in Table 5. ASTCT CRS consensus grading scale is provided in Section 10.15.

Table 5 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended IMP dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[a] • No hypotension • No hypoxia[b].	No dose modification of SAR444245[d]/cemiplimab[d]. Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the patient's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves
Grade 2 • Fever (Temperature ≥38°C)[a] • Hypotension not requiring vasopressors • And/or[b] hypoxia requiring low-flow nasal cannula[c] or blow-by	Temporarily interrupt both SAR444245 and cemiplimab, if events occur during the infusion. Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Increase monitoring of vital signs, cardiac and other organ functions closely as medically indicated until the participant recovers. Transfer to ICU may be required. For patients with comorbidities, older age, or with oxygen requirement, hypotension, or patients in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab should be considered, as per guidance for Grade 3 events. IMP may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.

Event severity (ASTCT CRS Consensus Grading)	Recommended IMP dose modification and supportive care guidelines
Grade 3 • Fever (Temperature ≥38°C)[a] • Hypotension requiring vasopressors • And/or[b] hypoxia requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	If CRS Grade 3, temporarily withheld both SAR444245 and cemiplimab, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at the dose below the current dose level or permanently discontinued, as clinically indicated. The participant can continue treatment with cemiplimab without dose modification. If subsequent administration is tolerated, resuming SAR444245 at the previous dose for subsequent administrations can be considered based on the clinical judgement of the Investigator with the Sponsor.
Grade 4 Life-threatening consequences; urgent intervention indicated • Fever (Temperature ≥38°C)[a] • Hypotension requiring multiple vasopressors • And/or[b] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 4, permanently discontinue SAR444245 and temporarily withhold or permanently discontinue cemiplimab. If temporarily interrupted, cemiplimab can be resumed without dose modification only when symptoms have resolved or improved to Grade 1. If Grade 3 or Grade 4, initiate IV corticosteroids (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed. CRS is considered resolved when there is sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS. If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, initiate management for persistent or worsening CRS. Re-evaluation for other contributing conditions will be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for patients weighing ≥30 kg) should be administered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension fever and other manifestations is observed after the first dose of tocilizumab, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. For participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab and steroids, alternative options will be discussed with clinical site specialists.

a Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at <6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

d Information for preparation and storage of SAR444245 and cemiplimab are provided in the pharmacy manual.

Abbreviations: AE=adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP= Bilevel Positive Airway Pressure; CPAP= Continuous Positive Airway Pressure; CRS=cytokine release syndrome; ICU=intensive care unit; IMP=investigational medicinal product; IV=intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.6.4.4 Immune-related adverse events

Cemiplimab may be associated with a unique set of toxicities termed immune-related adverse events (irAEs), and SAR444245 may increase the incidence and severity of these events.

IrAEs are thought to be caused by unstrained cellular immune responses directed at the normal host tissues and can occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment is critical to reduce complications.

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. For suspected irAEs, adequate evaluation should be performed to confirm etiology or exclude neoplastic, infectious, metabolic, toxin, or other etiologic causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Based on the emerging safety profile of cemiplimab and other antibodies targeting the PD1/PDL1 axis (38, 39), the following working case definitions are provided to help Investigators distinguish irAEs from non-immune AEs. These case definitions pertain to the more commonly reported irAEs associated with PD-1 inhibition (38, 39), and is not exhaustive of all possible irAEs. Clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events (40, 41) should be reviewed in participants with concerning presentations.

The case definitions below have not been validated and are intended only as guidance for investigators to help distinguish irAEs from non-immune AEs. Investigators' clinical judgment may include other factors when determining immune-relatedness. The case definitions for irAEs may evolve as clinical experience increases with cemiplimab and other antibodies targeting the PD-1/PD-L1 axis.

a. **Immune-related diarrhea/colitis**: These events are on a continuum, where diarrhea is defined as increased stool frequency and colitis involves abdominal pain and either clinical or radiologic evidence of colonic inflammation (38). Onset at 4 to 6 weeks is common (39). A CT scan usually demonstrates diffuse colitis (42). Exclude clostridium difficile or other infectious etiologies and laxative misuse.

b. **Immune-related encephalitis**: Patients may present with a variety of symptoms ranging from headache and word finding difficulties to seizures, altered mental status, and somnolence. Untreated, this syndrome can be fatal. Neurological consult is strongly encouraged, and therapy usually includes systemic corticosteroids.

c. **Immune-related hepatitis**: Laboratory studies are notable for elevated ALT and/or AST that is usually asymptomatic. Viral or other drug-induced hepatitis is excluded. Exclude alcohol-related liver toxicity. If clinically appropriate, consider radiologic imaging to exclude malignant causes. If clinically appropriate, exclude worsening of underlying cirrhosis.

d. **Immune-related hypophysitis**: Laboratory studies are notable for panhypopituitarism including low am cortisol with normal or low adrenocorticotropic hormone, low thyroid-stimulating hormone (TSH) with a low free T4, low luteinizing

hormone/follicle-stimulating hormone or testosterone (sex specific), and low prolactin. The most common side effect is headache, but side effects may also include fatigue, weakness, confusion, hallucinations, memory loss, labile mood, insomnia, anorexia, temperature intolerance, chills, decreased libido, and visual impairment. Untreated, this syndrome can be fatal. Treatment includes hormone replacement.

e. **Immune-related hypothyroidism**: Laboratory studies are notable for elevated TSH associated with low serum free thyroxine (free T4). If elevated TSH is detected, it is recommended that free T4 level also be tested. Elevated TSH with low free T4 establishes the diagnosis of hypothyroidism. Hypothyroidism may be asymptomatic or associated with symptoms such as fatigue, constipation, cold intolerance, dry skin, weight gain, and/or bradycardia. Exclude other causes of hypothyroidism, such as prior radiation therapy to the neck. In patients with prior history of hypothyroidism, exclude noncompliance with thyroid replacement medication.

f. **Immune-related hyperthyroidism**: Hyperthyroidism should be managed with standard antithyroid pharmacotherapy, and consultation with an endocrinologist is recommended.

g. **Immune-related mucositis:** Mucositis should be treated according to standard of care.

h. **Immune-related nephritis:** Nephritis can present with generalized edema and weight gain, and should be managed with diuretics. Consultation with a nephrologist is recommended.

i. **Immune-related pneumonitis**: Pneumonitis, defined as inflammation of the lung parenchyma, may present as shortness of breath, cough, fever, and/or chest pain. Median time from start of anti-PD-1 therapy to onset of pneumonitis is 2.6 months but delayed onset of pneumonitis has been reported. The most common radiologic pattern on CT chest has been described as cryptogenic organizing pneumonia (COP), but other radiographic patterns may occur. If performed, biopsy may demonstrate lymphocyte-predominant interstitial pneumonitis with areas of organizing pneumonia. Exclude infectious causes of pneumonitis.

j. **Immune-related rash**: Skin examination demonstrates a rash that is usually maculopapular, but other presentations may occur, including papulopustular, follicular, or urticarial dermatitis. Consider dermatologic consultation and biopsy for atypical presentations. Exclude other causes such as virally-induced rash or contact dermatitis.

k. **Immune-related uveitis:** Uveitis can present with redness of the eye, ocular pain, photosensitivity, and vision changes. Patients with uveitis should be urgently referred to ophthalmology for consultation and treatment.

Dose modification and toxicity management guidelines for irAEs are provided in Table 6. Of note, if the AE is considered immune-related, both drugs in the combination should be held according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed. Where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of cemiplimab as a monotherapy may be considered after communication with the Sponsor.

The CTCAE v 5.0 must be used to grade the severity of AEs.

Table 6 - Guidelines for the management of immune-related adverse reactions

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
Pneumonitis	Grade 1	Consider withholding[b]. May be continued with close monitoring	Consider withholding[b]. May be continued with close monitoring	• Radiologic findings should be followed on serial imaging studies at least every 3 weeks • Monitor for symptoms every 2-3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated • If SAR444245 and cemiplimab have been withheld, they can be restarted upon resolution and after corticosteroid taper, without dose modification.
	Grade 2	Withhold[b]	Withhold[b]	To rule out other causes such as infection: • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1-3 days If the patient is determined to have study drug associated pneumonitis: • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1-2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with SAR444245 and cemiplimab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. • **For recurring Grade 2 event**, SAR444245 may be either permanently discontinued or resumed at the dose below the current dose level after discussion with Sponsor, as clinically relevant, and cemiplimab withheld and resumed without dose modification, upon event resolution and after corticosteroid taper. Any additional recurrence should lead to permanent treatment discontinuation.

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
	Grade 3 and 4	Permanently discontinue	Permanently discontinue	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2 to 4 mg/kg per day prednisone or equivalent). When symptoms improve to Grade 1 or less, a high-dose oral steroid (1 to 2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab
Colitis[c]	Grade 1	No change in dose	No change in dose	• Ensure adequate hydration • For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and American Dietetic Association colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
	Grade 2	Withhold[b]	Withhold[b]	• Ensure adequate hydration • GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, SAR444245 and cemiplimab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or resolve, corticosteroid taper should be started and continued over at least 1 month.

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
	Grade 3	Withhold[b] OR Permanently discontinue if clinically necessary	Withhold[b]	• Ensure adequate hydration For Grade 3 to 4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or CT can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or resolve, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis[f] • If symptoms persist despite the above treatment a surgical consult should be obtained. • Treatment can only be resumed for Grade 3 event and if event has improved to Grade ≤1 within 12 weeks and after corticosteroid taper. SAR444245 can then be resumed at the dose below the current dose level after discussion between Investigator and Sponsor or be permanently discontinued if clinically necessary and cemiplimab can be resumed without dose modification. • For recurring Grade 3 event or for Grade 4 events, both IMP components should be permanently discontinued.
	Grade 4	Permanently discontinue	Permanently discontinue	
Hepatitis	Grade 2 (AST or ALT>3 to ≤5×ULN or total bilirubin >1.5 to ≤3×ULN[e])	Withhold[d]	Withhold[d]	• Initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper • Resume cemiplimab and SAR444245 if hepatitis improves and remain at Grade 0 - 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or return to baseline AST or ALT after completion of corticosteroid taper

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
	Grade ≥3 (AST or ALT >5×ULN or total bilirubin >3×ULN[e])	Permanently discontinue	Permanently discontinue	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. • Treat with high-dose IV glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity[f] • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
Endocrinopathies	Grades 2, 3, or 4	Withhold[b] if clinically necessary (no need to withhold for Grade 2 diabetes, Grade 2 hyperthyroidism, and all grades hypothyroidism)	Withhold[b] if clinically necessary (no need to withhold for Grade 2 diabetes or hyperthyroidism, and all grades hypothyroidism)	• Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging as appropriate for the management of the event, according the dysfunction observed • Replacement of appropriate hormones as required. Grade 3-4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis; hospitalization and IV methylprednisolone should be initiate • In situation when IMP is withheld, restarting of treatment should involve discussion with Investigator and Sponsor, and may require the input of specialty clinician. Restarting SAR444245 at dose below the current dose level may be considered. Cemiplimab should be restarted without dose modification.
Nephritis	Grade 1	Consider Withholding[b]. May be continued with close monitoring	Consider Withholding[b]. May be continued with close monitoring	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol.
	Grade 2	Withhold[b]	Consider Withholding[b]. May be continued with close monitoring	• Systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or resolve, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. If elevations persist >7 days or worsen, treat as Grade 4.

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
	Grade 3 and 4	Permanently discontinue	Permanently discontinued	• Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or resolve, steroid taper should be started and continued over no less than 4 weeks.
Uveitis	Grade 1	Withhold[b] OR Permanently discontinue if clinically necessary	Withhold[b] OR Permanently discontinue if clinically necessary	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. • Discontinue both SAR444245 and cemiplimab if symptoms persist despite treatment with topical immunosuppressive therapy.
	Grade 2	Permanently discontinue	Withhold[b] OR Permanently discontinue if clinically necessary	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. • Discontinue both SAR444245 and cemiplimab if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.
	Grade 3 and 4	Permanently discontinue	Permanently discontinue	• Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold[b] OR Permanently discontinue if clinically necessary	Withhold[b] OR Permanently discontinue if clinically necessary	• Consider specialty consultation whenever relevant • Corticosteroids administration as previously mentioned • Please refer to most recent guidelines (43, 44). • Grade 3 events that require full permanent discontinuation include, but are not limited to Guillain-Barré syndrome, encephalititis, Stevens-Johnson syndrome and toxic epidermal necrosis.
	Grade 4	Permanently discontinue	Permanently discontinue	

Event	Severity (NCI-CTCAE v 5.0)	Action with IMP		IMP dose modification details & Supportive care guidelines
		SAR444245[a]	Cemiplimab[a]	
Recurrent or persistent immune-mediated adverse reactions	Grade 2 or 3 persistent for ≥12 weeks after last IMP dose, recurrent Grade 3 or 4 events, and events requiring 10 mg per day or greater prednisone or equivalent lasting ≥12 weeks after last IMP dose	Permanently discontinue	Permanently discontinue	Please refer to above mentioned recommendations for the management of the recurring event.

a Information for preparation and storage of SAR444245 and cemiplimab are provided in the pharmacy manual
b Can be resumed if improvement to Grade ≤1 within 12 weeks and after corticosteroid taper.
c All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
d Can be resumed if improvement to Grade ≤1 or baseline within 12 weeks and after corticosteroid taper.
e Or above baseline. If baseline was abnormal as per NCI-CTCAE v 5.0.
f REMICADE (infliximab) prescribing information.
Abbreviations: CTCAE=common terminology criteria for adverse events; NCI=National Cancer Institute.

6.6.4.5 Immune cell-associated neurotoxicity syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome is a neuropsychiatric syndrome which is frequently associated with CRS; however; it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.15). Recommendations for ICANS management mainly include the use steroids, whereas tocilizumab should only be used in the context of CRS, as outlined in Table 7. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 7 - Guidelines for the management of immune cell-associated neurotoxicity syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	**Recommended IMP dose modification and supportive care guidelines**
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	Withhold SAR444245[a] and cemiplimab[a]. Initiate treatment with IV corticosteroids as needed. SAR444245 and/or cemiplimab may be resumed only after patient recovery or improvement to Grade 1 after corticosteroid taper. No modification in cemiplimab dose is recommended, and consideration for reduction of SAR444245 to the dose below the current dose level as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3: ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention.	If Grade 3 ICANS, withhold SAR444245 and cemiplimab. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at the dose below the current dose level or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. Treatment with cemiplimab can be restarted without dose modification. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 5. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days.

Event severity (ASTCT Consensus Grading criteria)	Recommended IMP dose modification and supportive care guidelines
Grade 4: ICE score: 0 (patient is unarousable and unable to perform ICE). Patients is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Signs of diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 4 ICANS, permanently discontinue SAR444245 and cemiplimab. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 5. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS: If there is no clinical improvement within 24 to 72 hours, re-evaluation for other contributing conditions should be done. Administration of IV **tocilizumab** at 8 mg/kg (for patients weighing ≥30 kg, total dose should not exceed 800 mg) should be considered, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant specialties should be involved whenever indicated.

a Information for preparation and storage of SAR444245 and cemiplimab are provided in the pharmacy manual
Abbreviations: AE=adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; EEG= electroencephalography; ICE=immune effector cell-associated encephalopathy; IV=intravenous.

6.6.4.6 Vascular leak syndrome (VLS)

Vascular Leak Syndrome is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following **clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic, shock with multiple-organ failure.** Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 8. These guidelines are not comprehensive and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (45).

Table 8 - Guidelines for the management of vascular leak syndrome (VLS)

Event severity (NCI-CTCAE v 5.0[a])	Recommended IMP dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	IMP should be withheld. Upon resolution of VLS or improvement to Grade 1, SAR444245[b] can be resumed at the dose below the current dose level, and cemiplimab[b] can be resumed without dose reduction. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, SAR444245 should be permanently discontinued. The participant can continue treatment with cemiplimab upon resolution of the event or improvement to Grade 1. In patients with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-specific therapy should be initiated as soon as possible to facilitate recovery. During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a In NCI-CTCAE v 5.0 Vascular leak syndrome referred to as Capillary leak syndrome.
b Information for preparation and storage of SAR444245 and cemiplimab are provided in the pharmacy manual.
Abbreviations: AE=adverse event; CTCAE=common terminology criteria for adverse events; IV=intravenous; NCI=National Cancer Institute.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

There will be no intervention beyond the end of the study.

6.8 TREATMENT OF OVERDOSE

There is no specific antidote for overdose with SAR444245 or cemiplimab.

If overdose occurs (see Section 8.3.8 for definition), symptomatic management is indicated.

Treatment of overdose should consist of general supportive care with aggressive fluid management, if clinically indicated.

Procedures for treating symptoms and complications of immune-related adverse events are provided in Section 6.6.4.4.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 90 days).
3. Obtain a plasma sample for PK analysis right after the overdose event is identified (only if an overdose is identified within 5 days from start of overdose infusion).
4. Document appropriately in the e-CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Study intervention should be permanently discontinued in any of the following cases:

- At the participant's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative (if allowed by local regulations). "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the patient's participation in the procedure(s) involved in the research.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Unacceptable AE.
  - Documented disease progression (including both radiological PD and clinical PD).
    - [redacted] *Clinical Stability is defined as:1) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) indicating disease progression. 2) No decline in ECOG performance status. 3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.*
  - Poor compliance to the study protocol.
  - Other, such as concurrent illness, that prevents further administration of study intervention, or that in the Investigator's opinion, in the best interest of the participant
- In case of pregnancy occurrence

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for serial tumor assessment if permanent discontinuation is not due to PD, for safety assessment as per SoA (Section 1.3) and until resolution or stabilization of AE, and any other assessment as per SoA. Data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed are reported in the SoA.

7.1.1.1 Unacceptable adverse events leading to permanent intervention discontinuation

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Table 6, or if the Investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Any potentially clinically significant abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation and repeated after 24 hours to document evolution before making a decision of permanent intervention discontinuation for the concerned participant.

Decision criteria for discontinuation following immune-mediated AEs are described in Section 6.6.4 (Guidelines for the management of IRR, CRS, ICANS, VLS).

If participants are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, they will be maintained on treatment.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent intervention discontinuation, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate. Tumor assessment should be repeated if not done at the last cycle. A biopsy (optional - special consent) may be performed if treatment is discontinued for disease progression following an initial response.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 13 Section 10.13: Contingency Measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

7.1.3 Rechallenge

Re-initiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met.

Recommendations for rechallenge in the context of an epidemic/pandemic (eg, COVID-19), are included in Appendix 13: Contingency Measures for a regional or national emergency (Section 10.13) that is declared by a governmental agency.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the treatment, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have been withdrawn from the study treatment cannot be re-included in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures are summarized in this section and their timing is presented in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- During the screening period, demography, medical/surgical, and disease history will be evaluated. Demography includes age, gender, race, and ethnicity. Medical/surgical history includes relevant history of previous pathologies and smoking status. Disease history includes stage at diagnosis and at study entry, and previous anti-tumor therapy (type, duration, reason for discontinuation and response to the therapy). In addition, results of driver gene mutation (such as *BRAFV600E* for participants with melanoma) are also to be collected.
- A comprehensive medical history will be assessed for any cardiovascular signs or symptoms prior to treatment, along with a baseline ECG, echocardiogram and troponin level.
- Regular blood samples will be collected from each participant throughout the duration of the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Details on blood sampling, including the estimated volume collected for each analysis are provided in the laboratory manual.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.13.

8.1 EFFICACY ASSESSMENTS

The assessment of anti-tumor activity documented by objective response to the IMP is the primary endpoint for this study and is conducted as per schedule provided in the SoA. All participants treated must have at least one measurable lesion for inclusion.

Decision to pursue treatment will be based on the response evaluation made by the Investigator, however, measures of lesions will be collected in the e-CRF for a determination of response by the Sponsor. A partial or complete response must be confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy. Confirmation of PD using [redacted] may be done at the discretion of the Investigator when clinically indicated. Please refer to Section 7.1.1 for details on documented disease progression.

Investigators will obtain copies of the images and will provide them to Sponsor or other repository facility identified by the Sponsor for potential central review. Images (scans and/or medical photographs) and pathological reports when relevant for confirmation of CR or characterization of a new skin lesion in locally advanced CSCC will be prospectively collected for potential retrospective central analysis; the prospective collection of these materials can be cancelled at any time.

Assessment of tumor response will be conducted using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, modified WHO criteria, or composite response criteria (see Section 10.8 and Section 10.9) according to the nature of the measurable lesions, as described below.

8.1.1 Assessment of objective response using the most appropriate modality according to the nature of the measurable lesion(s)

For participants with disease that can be measured radiologically according to RECIST 1.1 criteria (Section 10.8), a CT or MRI for tumor assessment will be performed as detailed in Section 1.3. The choice of whether the imaging is by CT or MRI is an investigator decision, but preferred imaging choices are provided in below. Once the choice of CT scan or MRI has been made, subsequent assessments should be made using the same modality. For participants whose CSCC lesions are evaluable on the skin, composite response criteria (Section 10.9) should be used on the same schedule, in combination with radiologic imaging if appropriate. Brain MRI is required at screening if not performed in the prior 60 days. For participants with CSCC, baseline brain imaging is only indicated in the presence of clinical suspicion of brain metastases. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated.

- **For Cohort A and Cohort B Participants with metastatic disease**: Baseline imaging should include all known target lesions. Baseline scans must evaluate extent of disease, including imaging of chest, abdomen, and pelvis. This may be accomplished with CT chest, abdomen, and pelvis with contrast, or CT chest with contrast and MRI abdomen/pelvis with gadolinium. The imaging modality for metastatic lesions may be either CT with iodinated contrast or MRI with gadolinium, per investigator discretion. Magnetic resonance imaging with gadolinium is generally preferred for bone lesions, perineural lesions, abdomen, pelvis, extremity, and head and neck. Computed tomography with contrast is generally preferred for chest. For participants who also have externally visible lesions, digital medical photography will be used, and these lesions generally will be followed as non-target lesions. Whole-body imaging, as performed at the baseline assessment, is strongly recommended at each response assessment. At a minimum, all radiologically measurable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment. Additionally, radiologic imaging of anatomic area of externally visible target lesions should be performed at baseline and at each response assessment (MRI with gadolinium is preferred for all anatomic sites except lung). Externally visible CSCC lesions noted at baseline should be photographed at each response assessment (Section 10.12) and will generally be deemed non-target. New externally visible lesions that are clinically suspicious for malignancy should be photographed (Section 10.12) and

biopsied. **Note:** In participants with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated.

- **For CSCC participants with locally advanced skin lesions and skin metastases**: Externally visible lesions will be followed by digital medical photography. Baseline assessments will include radiologic imaging of all target lesions (preferably MRI with gadolinium for all anatomic sites except lung, but CT with iodinated contrast allowed at any anatomic site, per investigator discretion) to assess for deep invasion. All externally visible CSCC lesions should be photographed **in** a consistent manner at each response assessment as described in Section 10.12. Radiologic imaging (MRI with gadolinium preferred) of anatomic area of externally visible target lesions should be performed at each response assessment. In cases in which it is the opinion of the Investigator that no significant added information was provided by anyone of the radiologic imaging or digital medical photography modality, it is allowed to use either one of these at subsequent response assessments of that lesion, at the discretion of the Investigator.

[redacted]

[redacted]

For participants with non-skin metastatic disease, participants will generally be followed by RECIST 1.1 criteria (Section 10.8). It is possible that some of these participants may also have externally visible lesions that are measurable by digital medical photography. Generally, it will be clinically appropriate to follow these externally visible lesions as non-targets. However, for these participants with externally visible lesions that are deemed clinically significant by the investigator, the clinical and composite response criteria in Section 10.9 may be used in selected cases. However, it is anticipated that most participants with metastatic disease will be followed by RECIST 1.1 only.

For participants with locally advanced skin lesions and skin metastasis, response assessment is according to the clinical and composite response criteria in Section 10.9. For externally visible lesions that are indeterminate appearing regarding presence of CSCC, see Section 10.11 for guidelines on tumor biopsies.

All radiology, photography and biopsy reports will be collected centrally for potential independent central review to determine overall response for each participant based on the integration of these modalities.

8.2 SAFETY ASSESSMENTS

The main anticipated adverse effect for the combination of SAR444245 with cemiplimab includes manifestations of cytokine release that can range from fever to hypoxia to hypotension, with or without manifestations that may include any of the organ systems. These mild events occur between around 12 to 18 hours after the first administration and a more intensive monitoring of vital signs is planned during that period. Targeted physical exams and standard laboratory tests will be conducted to monitor potential changes in the main body functions. Measurement of cytokines in plasma are planned at relevant timepoints. White blood cell differential count will be measured to monitor for transient lymphopenia which is commonly observed in the first few days following SAR444245 infusion. Eosinophilia that is surrogate to VLS will also be monitored. IL-5, which is also a marker of VLS, will be included in the PDy cytokine panel. Combining SAR444245 with cemiplimab may increase the frequency and severity of immune-related adverse events related to cemiplimab. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level will be monitored. When clinically indicated, on-treatment ECG and LVEF will be assessed and compared to baseline. More details on the safety assessment are provided below. Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A full physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Neurological and skin systems. Height and weight will also be measured and recorded.
- A directed physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses. Investigators should also pay attention to clinical signs suggestive of VLS, such as peripheral edema, pericardial effusion and pleural effusion, as well as clinical signs suggestive of immune-related adverse events, such as pneumonitis, colitis, endocrinopathies, to name a few. Complementary assessments should be performed to establish the diagnosis when clinically indicated. Early signs of cytokine release syndrome should also prompt a thorough clinical assessment to identify the involvement of a specific organ system, including neurological system.

8.2.2 Vital signs

- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

- Vital signs should be taken pre-dose as per SoA and repeated as clinically indicated at Investigator's discretion during and after study medication administration.
- **At Cycle 1 Day 1**, vital signs after infusion initiation will be collected more intensively;
  - **For the participants of dose escalation** vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an inpatient setting.
  - **For other participants**, vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose. At Investigator's discretion, participants (not in the dose escalation) may have intensive vital sign monitoring.
- From Cycle 2 and beyond study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, 4 to 6 hours post-dose, or as clinically indicated.

8.2.3 Electrocardiograms and LVEF

- Includes single 12-lead ECG and LVEF that will be performed at screening and then, as clinically indicated.
- Triplicate 12-lead ECG will be obtained when indicated, for instance to further document a QTc prolongation, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- Each time a triplicate ECG is required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- LVEF evaluation will be done by echocardiography or multigated acquisition (MUGA), and any repeated assessment should be done with the same technology used at screening.
- Additional evaluations such as ECG, LVEF, Holter monitoring, cardiac enzymes (such as troponin) and consultation with a cardiologist should be done when clinically indicated.
- During treatment, or post treatment follow-up: In case of a suspicion of a drug related cardiac event (eg, including signs/symptoms of cardiac disease, ECG and/or echo changes, troponin elevation, etc), Investigators are encouraged to do ECG, echocardiography and/or cardiac biomarker tests, as medically indicated, including cardiology consultation.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The clinical safety laboratory assessments will be done in the local laboratory.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the

underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within Follow-Up Visit 1 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
- Women of childbearing potential must have a negative urine pregnancy test result within 7 days prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 180 days after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.8.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative if allowed by local regulations).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, including adverse events of new onset, as well as worsening of baseline signs and symptoms will be collected throughout study period, from the signing of the informed consent form (ICF) until **30 days** following last administration of study treatment.

All SAEs and AESIs will be collected throughout study period, from the signing of the informed consent form (ICF) until **90 days** following last administration of study treatment.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3) (See instructions specific for participants in Germany in Appendix 7, Section 10.7). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AESIs (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Stabilization is defined as an AE ongoing without any change for at least 3 months. Participants with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or starting of a new antineoplastic therapy, whichever occurs first.

Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements

relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- Serious adverse events that are considered expected will be specified in the reference safety information (IB for SAR444245 and SmPC for Libtayo [cemiplimab]).
  - Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, should be expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 180 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates another anticancer therapy.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Cardiovascular and death events

Cardiovascular events that meet AESI criteria should be reported as such (see Section 8.3.8 for details.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

An adverse event of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.
The following events need to be reported as AESIs:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.3).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 10.4).
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - Infusion of IMP: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
  - An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow-up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet

the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor.

- **Other project specific AESIs**
  - IRR Grade ≥2
  - CRS Grade ≥2
  - ICANS of any grade
  - VLS of any grade
  - SARS-CoV-2 infection/COVID-19 disease
  - Any immune-related AE Grade ≥3
  - Arrhythmia Grade ≥3

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

No PK parameters will be assessed, as only sparse sampling for pharmacokinetic concentrations of SAR444245 and cemiplimab is implemented in the study.

The sampling time-points for PK and ADA for/against SAR444245 and/or other IMPs may be updated during the course of the study, based on the updated knowledge of drug behavior, upon notification from the Sponsor.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded while for samples to be collected at time of biomarker sampling, no specific time on the given day is necessary.

Instructions on the collection, processing, storage, and shipment of samples will be provided in the laboratory manual. Sample analysis will be performed at a laboratory designated by the Sponsor.

Samples collected for analyses of SAR444245 or cemiplimab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study and any remaining plasma/serum volume may also be used for further exploratory analysis if deemed relevant.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for details of pharmacodynamics biomarker.

8.6 GENETICS AND/OR PHARMACOGENOMICS

[redacted]

8.7 BIOMARKERS

[redacted]

[redacted]

8.8 IMMUNOGENICITY ASSESSMENTS

The sampling time points for ADAs may be reduced or increased during the course of the study based on the updated knowledge of drug behavior and its immunogenicity, upon notification from the Sponsor.

Samples for the immunogenicity assessment of SAR444245 will be collected according to the PK flowcharts. Instructions for the collection and handling of biological samples will be provided by the Sponsor. Sample analysis will be performed at a laboratory designated by the Sponsor.

Samples will be screened and then confirmed for anti-drug antibodies and the titer of confirmed positive samples will be reported. Additional analyses may be performed to further characterize the immunogenicity of SAR444245.

Anti-drug antibody samples remaining after determination of immunogenicity may be kept for possible exploratory analysis of biomarkers. The exploratory data will not be included in the study report but will be kept on file.

8.9 HEALTH ECONOMICS

No health economics data will be collected.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The two independent cohorts of the study are designed to obtain antitumor activity, safety pharmacokinetic (PK) and pharmacodynamic (PDy) data on SAR444245 administered in combination with cemiplimab to participants with advanced unresectable or metastatic skin cancers.

The study is designed to assess clinical benefit of SAR444245 when combined with cemiplimab in the two indications of interest. As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design. No formal testing procedure is going to be considered.

9.2 SAMPLE SIZE DETERMINATION

The study will start with a **dose escalation** to determine the RP2D of SAR444245 when combined with cemiplimab.

The plan is to treat approximately 40 participants in Cohort A and 40 participants in Cohort B at the RP2D.

Table 9 lists estimated ORR and the corresponding 90% exact CIs by number of responders from a sample size of 40 participants exposed in Cohort A and in Cohort B.

Table 9 - Cohort A and B: Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
18	45.0% (31.5% - 59.1%)
20	50.0% (36.1% - 63.9%)
22	55.0% (40.9% - 68.5%)
24	60.0% (45.8% - 73.1%)
26	65.0% (50.8% - 77.5%)

CI: confidence interval

For each Cohort A and Cohort B individually, with a sample size of 40 study participants, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this study.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 10):

Table 10 - Populations for analyses

Population	Description
Exposed	Exposed population will include all participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 or cemiplimab).
Efficacy	Efficacy population will include all participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.
DLT-evaluable	DLT-evaluable population will include all participants in the dose escalation who have been treated and observed for at least 21 days. Any participants who have experienced a DLT during DLT observation period will also be DLT-evaluable.
PK	The PK population will include all participants from the exposed population with at least 1 PK concentration available after the first dose of study intervention.
PDy	The PDy population will include all participants from the exposed population with at least 1 PDy parameter assessed after the first dose of study intervention.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, key secondary endpoints and exploratory endpoints.

9.4.1 General considerations

This study is not intended to explicitly test a hypothesis, and 90% confidence interval (CI) will be provided for primary and secondary efficacy endpoints for descriptive purpose only.

All efficacy analyses will be performed on the efficacy population and analyzed by cohort and by dose (as applicable). Objective response rate, as well as PFS, DOR, and CBR will be derived using the local radiologist's/Investigator's assessment for both cohorts.

All safety analyses will be performed on the exposed population by cohort, by dose (if applicable) and overall (if applicable). The baseline value will be defined as the latest value or measurement taken up to the first administration of the IMP.

The analysis period will be divided into 3 segments:

- The pre-treatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The on-treatment period (ie, treatment-emergent period) is defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.
- The post-treatment period is defined as the time from the 31 days after the last administration of IMP.

9.4.2 Primary endpoint(s)

9.4.2.1 Objective response rate

The primary endpoint is the ORR. Central imaging may be done retrospectively if significant activity is observed.

For Cohort A (melanoma), the ORR is defined as the proportion of participants who have a confirmed CR or PR determined by Investigator per RECIST 1.1.

For Cohort B (CSCC), the ORR is defined as the proportion of participants who have a confirmed CR or PR determined by Investigator per RECIST 1.1, or modified WHO criteria for medical photographs of external skin lesions, or composite criteria.

The BOR is the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anti-cancer therapy, whichever occurs first.

The ORR and the BOR will be summarized with descriptive statistics. In addition, two-sided 90% CIs will be computed using the Clopper-Pearson method.

9.4.3 Secondary endpoint(s)

The secondary endpoints include safety, efficacy (CRR, DOR, CBR, PFS per RECIST 1.1 or modified WHO criteria, or composite criteria when relevant), immunogenicity, and PK.

9.4.3.1 Complete response rate

For Cohort A (melanoma), CRR is defined as the proportion of participants from the analysis population who have a confirmed CR determined by Investigator per RECIST 1.1.

For Cohort B (CSCC), CRR is defined as the proportion of participants from the analysis population who have a confirmed CR determined by Investigator per RECIST 1.1, or modified WHO criteria for photographs of external skin lesions, or composite criteria.

9.4.3.2 Time to complete response

Time to CR will be assessed on the subgroup of participants who achieved confirmed CR for melanoma participants and when applicable for CSCC participants.

Time to CR will be defined as the time from the first administration of 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 or modified WHO criteria for medical photographs, or composite criteria, whichever relevant.

9.4.3.3 Time to response

Time to Response will be assessed on the subgroup of participants who have achieved confirmed objective response.

Time to Response will be 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 RECIST1.1 or modified WHO criteria for medical photographs, or composite criteria, whichever relevant.

9.4.3.4 Duration of response

The DOR will only be summarized on the subgroup of participants who have achieved confirmed objective response.

The DOR will be defined as the time from the first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed to the date of first documentation of objective PD determined by Investigator per RECIST 1.1 or modified WHO Criteria for medical photographs or composite criteria when relevant before the initiation of any post-treatment anti-cancer therapy or death due to any cause, whichever occurs first.

In the absence of disease progression or death before the cut-off date, DOR will be censored at the date of the last valid tumor assessment performed before the cut-off date or date of initiation of new anti-cancer therapy, whichever is earlier. Duration of response will be summarized by cohort with descriptive statistics using Kaplan-Meier methods. The median DOR and associated 90% CI will be provided.

9.4.3.5 Clinical benefit rate

The CBR is defined as the proportion of participants with clinical benefit (confirmed CR or PR as BOR, or SD lasting at least 6 months, determined by Investigator per RECIST 1.1 or modified WHO Criteria for medical photographs or composite criteria, whichever relevant). For participants with measurable disease at baseline, they will be considered as clinical benefit responders if they achieve a CR or PR as BOR, or SD with an overall response recorded as SD at 6 months (ie, 26 weeks or later from first IMP intake, allowing for the ±7 days visit window for tumor assessment scheduled at 27 weeks).

9.4.3.6 Progression-free survival

Progression-free survival is defined as the time from the date of first IMP to the date of the first documentation of objective progressive disease 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.

The analysis of PFS will be based on the following censoring rules:

- If progression or death is not observed before the cut-off date and prior to the initiation of a further anti-cancer therapy, then PFS will be censored at the date of the last valid tumor assessment performed before the cut-off date or date of initiation of a further anti-cancer therapy, whichever is earlier.
- A participant without event (death or disease progression) and without any valid post-baseline tumor assessment will be censored at the day of first IMP (Day 1).

Progression-free survival will be summarized using Kaplan-Meier methods. The median PFS times and associated 90% CI will be provided.

9.4.3.7 Adverse events

All AEs will be classified by SOC and Preferred Term (PT) according to the latest available version of the medical dictionary for regulatory activities (MedDRA) and will all be categorized according to NCI-CTCAE v 5.0, except for CRS and ICANs events, for which severity will be categorized using ASTCT Consensus Grading.

- Pre-treatment AEs are defined as any AEs occurring during the pre-treatment period.
- Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator's opinion), or become serious during the on-treatment period.
- Post-treatment AEs are defined as AEs that are reported during the post-treatment period.

For participants with multiple occurrences of the same PT, the maximum grade will be used.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

Treatment-emergent adverse events:

An overall summary of TEAEs will be provided. The number and percentage of participants experiencing any of the following will be provided:

- TEAEs.
- TEAEs of Grade ≥3.
- Grade 5 TEAE (any TEAE with a fatal outcome during the on-treatment period).
- Serious TEAEs.
- Serious treatment-related TEAEs (for each individual drug).
- TEAE leading to permanent partial intervention discontinuation (for each individual drug).
- TEAE leading to full intervention discontinuation.
- Treatment-related TEAEs (for each individual drug).
- Treatment-related TEAEs of Grade ≥3 (for each individual drug).

Number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE v 5.0 grade (all grades and Grade ≥3) for the exposed population. Missing grades, if any, will be included in the "all grades" category. Similar summaries will be prepared for TEAEs related to SAR444245 and those related to cemiplimab, TEAEs leading to permanent partial intervention discontinuation, TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.

The following deaths summaries will be generated:

- Number and percentage of participants who died by study period (treatment, post-treatment) and reasons for death (disease progression, AE, or other reason).
- All TEAEs leading to death by primary SOC and PT showing number and percentage (%) of participants.

9.4.3.8 Clinical laboratory evaluations

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

When relevant, for laboratory variables, descriptive statistics for results and changes from baseline will be provided for the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using local measurements for laboratory variables.

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v 5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be provided for the exposed population.

When the NCI-CTCAE v 5.0 grading scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

For laboratory variables graded by NCI-CTCAE

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

9.4.3.9 Other secondary endpoints

Immunogenicity analyses will be described in the SAP finalized before database lock. The PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

Concentrations of each cohort by SAR444245 and cemiplimab will be summarized with descriptive statistics.

9.4.4 Tertiary/exploratory endpoint(s)

9.4.4.1 Exploratory antitumor indicators

[redacted]

9.4.4.2 Biomarker endpoints

[redacted]

9.4.5 Other safety analyse(s)

All safety analyses will be made on the exposed population. When relevant, the summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for baseline, last on treatment value and/or worst value.

9.4.6 Other analyse(s)

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.13.

9.5 INTERIM ANALYSES

No formal interim analyses are planned. However, at the end of the dose escalation, the occurrence of DLT and other safety data will be reviewed by SB to determine the RP2D.

After the dose is confirmed by the SB, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the DMC. The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. DMC will review safety data periodically. Ad hoc DMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other SAR444245 studies. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

In addition, for each cohort, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the study, eg, after 20 participants have undergone at least two post-baseline tumor assessment or have discontinued study treatment, whichever is earlier.

The cohort cut-off for the primary ORR endpoint analysis corresponds to approximately 9 months from the date of the last participant's first infusion (to document that last participant response is maintained for 6 months).

After the cohort cut-off date for the primary ORR analysis, participants can continue to receive IMP, if clinical benefit is observed, until full permanent discontinuation criteria described in Section 7 are met and will continue to undergo all assessments as per the study schedule of activities.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 3 years from cohort last patient-in (LPI).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative (if allowed by local regulations), and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 13: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.

- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other phamaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee structure

Data Monitoring Committee

Independent from the Sponsor and Investigators, the DMC role will monitor the safety of the participants enrolled in the study (ie, exposed to study treatment and/or to study procedures) and to provide the Sponsor with appropriate recommendations in due time to ensure the safety of the participants.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or e-CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the e-CRF.
- Guidance on completion of CRFs will be provided in the relevant Sponsor data management study document.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the e-CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the e-CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study or one or more cohorts at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study or cohort termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For cohort termination:
  - Early evidence for lack of benefit
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study or cohort is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. He/she should also stop all screening activities pertaining to the study or the relevant cohort(s). If there is a decision of the

Sponsor to pause recruitment in a cohort to allow decision making, then the Investigator should pause all screening activities until further notice.

If the cohort/study is early terminated the patients who are receiving and benefitting from study treatment as per Investigator judgment may continue study treatment until protocol defined treatment discontinuation criteria are met. The patients who continue study treatment after early study termination should be followed for safety (ie, study treatment administrations, ongoing SAE/related AE, new related AE, AESI or SAE and their associated concomitant medications and lab if any) and end of treatment reason during this time period.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 11 will be performed by local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 11 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology[a]	Platelet count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[b]	Urea or blood urea nitrogen (BUN)

Laboratory assessments	Parameters
	Creatinine and eGFR (MDRD formula[c])
	Glucose
	Potassium
	Sodium
	Calcium
	Phosphate
	Chloride
	Magnesium
	Bicarbonate[d]
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and direct bilirubin
	Total protein
	Lactate dehydrogenase (LDH)
	Albumin
	Amylase
	Lipase
Endocrine function tests[e]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT])
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, and leukocytes by dipstick
	Microscopic examination (if blood or protein is abnormal)
Other screening tests	• Follicle-stimulating hormone and estradiol may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[f] • Serology (hepatitis B surface antigen [HBsAg], hepatitis C virus antibody), Hepatitis B viral load, HCV RNA level, CD4 counts & HIV viral Load[g] • Troponin • The results of each test must be entered into the e-CRF.

NOTES:

a Hematology will be performed every cycle up to Cycle 12, then every other cycle during Treatment Period, except for WBC with differential that is to be done on D1 pre-dose, D2, D3, D8 and D15 during Cycle 1. If Grade 4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x 10^9/L. During the Observation Period, hematology will be performed at Follow-Up Visit 1.

b Blood Chemistry should be done with an overnight fasting if possible, (should not interfere with hydration requirements). It will be performed weekly on D1 pre-dose, D2, D8 and D15 during Cycle 1, then every cycle up to Cycle 12, then every other cycle during Treatment Phase. For participants in the dose escalation part, it will be also performed at D3. During the Observation Period, it will be performed at Follow-Up Visit 1. It can also be performed as clinically indicated. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

c Modification of Diet in Renal Disease (MDRD) equation: Glomerular filtration rate (mL/min/1.73 m2) = 175 × (Serum Creatinine)-1.154 × (Age)-0.203 × (0.742 if Female) × (1.212 if African American).

d Bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated)

e Endocrine function tests will be performed every 2 cycles until Cycle 12 (ie, Cycles 2, 4, 6, 8, 10 and 12). During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

f Pregnancy Test: Women of childbearing potential must have a negative urine pregnancy test result within 7 days prior to IMP administration of each cycle, at EOT and every 30 (±7) days until 180 days after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

g Participants with known HIV infection under antiretroviral treatment should have HIV viral load & CD4+ count done at baseline to confirm controlled infection. Participants with known HBV hepatitis under treatment must have viral load determined at baseline to document controlled infection. Participants with positive serology against HCV must have determination of HCV RNA levels. The need for additional testing due to positive test results will be at the discretion of the Investigator. HIV serology at screening will only be tested in any countries where mandatory as per local requirements.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
  - Development of drug dependence or drug abuse
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions

The purpose of the seriousness criteria listed above is to guide regulatory reporting obligations by the Sponsor. The Sponsor is required to expedite serious unexpected adverse reactions to regulatory health authorities and Investigators.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the e-CRF.

- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE e-CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, as per NCI CTCAE v 5.0 definitions:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of causality

- The Investigator should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment SAR444245, cemiplimab or the combination.
- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed e-CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor's representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours (refer to Section 10.7 for country-specific requirements for Germany).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator study file.

SAE reporting to the Sponsor's representative via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator study file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova up to 180 days and sperm up to 210 days (see inclusion criteria).

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)
- Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]

- Oral
- Intravaginal
- Transdermal
- Injectable

Progestogen-only hormone contraception associated with inhibition of ovulation[c]

- Oral
- Injectable

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: GENETICS

[redacted]

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

France

In France, the eligibility of patients to take part in the study is to be validated at the Multidisciplinary Collegial Meeting.

In France participants with BRAF-mutant melanoma will not be included in Cohort A (See Inclusion criterion I02, Section 5.1).

Ireland

In Ireland Cohort A will not be open to enrollment (See Inclusion criterion I02, Section 5.1).

Germany

For the sites in Germany, the Investigator must inform the Sponsor in case of a SAE/AESI immediately, after becoming aware without undue delay (see Section 8.3.1).

10.8 APPENDIX 8: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 (1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Confirmatory scans should also be obtained **at least 4 weeks** following initial documentation of objective response.

Selection of Lesions

- **Measurable disease**: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest X-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
- **Malignant lymph nodes**: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Target lesions**: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved

organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions**: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions**. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest X-ray**. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI**. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT**. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **Ultrasound**. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers**. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology**. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- **FDG-PET**. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible “new” disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A “positive” FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR)**: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD)**: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR)**: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD**: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD)**: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (1) are summarized in the table:

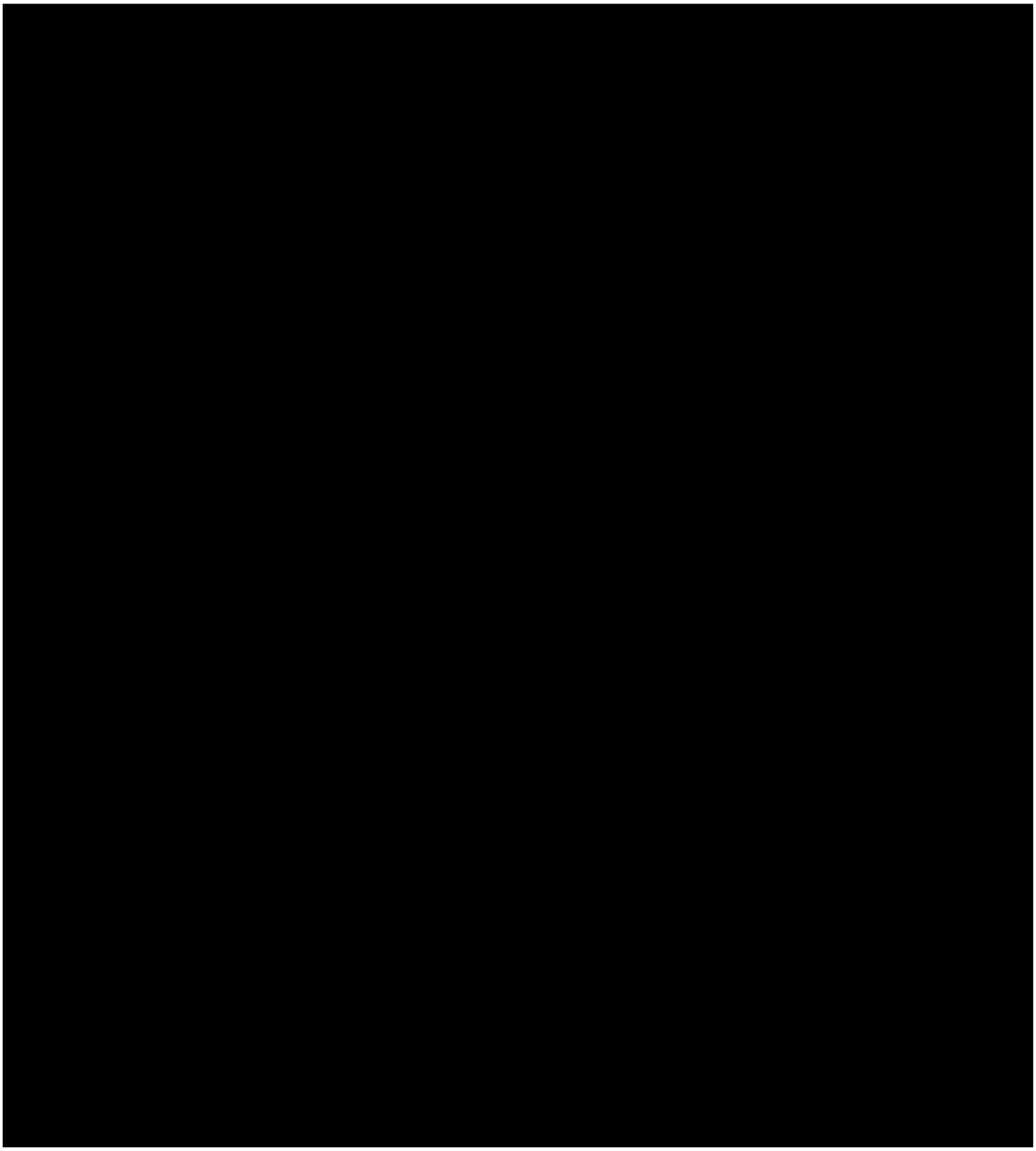
Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	>4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	>4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once >4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR = Complete response; NE = inevaluable; PD = Progressive disease; PR = Partial response; SD = Stable disease.
a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

10.9 APPENDIX 9: [redacted]

[redacted]



10.9.1 Response and stable disease duration (RECIST 1.1 and [redacted])

Response duration will be measured from the time measurement criteria for CR/PR[redacted] (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.9.2 Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion."

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case (1). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or SD and PD.

10.10 APPENDIX 10: WHO CRITERIA FOR DIGITAL MEDICAL PHOTOGRAPHS AND COMPOSITE RESPONSE CRITERIA FOR PARTICIPANTS WITH LOCALLY ADVANCED CSCC

This appendix describes clinical response criteria for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and RECIST 1.1.

Participants will be followed by digital medical photography and will also undergo radiologic imaging (typically, MRI with gadolinium) at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging (preferably, MRI with gadolinium) will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by digital medical photography. See protocol Section 8 for further information on imaging requirements.

Response assessments occur every 9 weeks up to Week 45, and every 12 weeks thereafter. Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. Guidelines for digital medical photography are provided in Appendix 12 (Section 10.12). Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMORS:

1) Anatomic Defects

Regarding tumor around a surgical cavity/anatomic defect (eg, rhinectomey), such lesions should be considered non-measurable unless there is a nodular lesion measuring ≥10 mm in maximal

bi-dimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered in measuring the lesion.

2) Indeterminate-Appearing Tissue

If there is uncertainty about whether a given lesion or area of a lesion represents malignancy versus benign process (eg, scarring, fibrosis), biopsies should be obtained. Indeterminate-appearing areas (eg, scarring, fibrosis) are included in the tumor measurements unless biopsies are obtained to establish benign status.

To reduce risk of sample error, biopsy of only a single area on the tumor is not allowed. Biopsy of at least two separate areas of the lesion are required when biopsy is indicated. Each biopsy will be performed in a pairwise manner (approximately adjacent) so that there will be one sample for local review and one for central review for each biopsy, as per Appendix 11 (Section 10.11).

As such, when the decision is made to perform biopsy, at least 4 biopsy samples are obtained (biopsy of two separate areas, with two biopsies in each area: one for central review, one for local review from each area). Biopsy samples will not be bisected or split in half for local and central review; rather, separate adjacent samples will be obtained. See Appendix 11 for biopsy details.

Note on timeline for finalization of measurement/response assessment: Generally, baseline disease measurements and response assessments should be completed on the day of the visit at which digital medical photography was performed. However, for visits in which tumor biopsies are performed, it is understood that the local pathology report may not be available for up to 5 business days after the biopsy.

When biopsies are performed to distinguish between benign versus malignant tissue, the annotated photograph for that visit should clearly indicate the region of the tumor that was biopsied to distinguish benign versus malignant tissue. Within one week of the date of biopsies, the investigator should finalize the tumor measurements for that visit with the benefit of the local pathology report.

For circumstances in which the intent of the biopsy is to distinguish between disease stability and response, it is not necessary to hold study treatment while the local pathology report is pending. For circumstances in which the biopsy, if positive, would result in discontinuation of study treatment due to progression, treatment should be held until biopsy results are finalized and progression has been ruled out.

3) Local Versus Central Review

De-identified digital medical photography results, biopsy results (Cohort B) as well as scans when relevant (Cohort A & B) will be collected prospectively for potential central review to provide response assessments as required by the Sponsor to address study objectives (Section 3). The prospective collection of these materials may be cancelled by the Sponsor at any time during the study. Clinical management decisions will be as per Investigator response assessments and local pathology review.

4) Confirmation of Responses

After any objective response, confirmatory digital photography (and radiologic imaging, if performed as part of the initial response assessment) will be obtained at least 4 weeks following initial documentation of objective response. Confirmatory biopsies are not required for partial response.

5) Participants with Externally Visible Tumors

Participants with metastatic CSCC will generally be followed by RECIST 1.1 criteria (Appendix 8). It is possible that some patients may also have externally visible lesions that are measurable by digital medical photography. In such circumstances, the externally visible lesions generally will be followed as non-target lesions. The exception to this rule would be a patient with externally visible lesions in whom the only M1 lesions are not measurable by RECIST (eg, a patient with bone-only metastases), in which case the externally visible lesions (lesion size ≥10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix, and the non-measurable metastatic lesions (eg, bone metastases) would be followed as non-target lesions.

Clinical Response Criteria for Externally Visible Tumors (for all patients with locally advanced CSCC)

Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension - at each tumor assessment and will be documented using standardized digital photography (Appendix 12). In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

Clinical response criteria for externally visible tumor(s) require bidimensional measurements according to WHO criteria and are as follows:

- Complete response of externally visible disease (vCR): all target lesion(s) no longer visible, maintained for at least 4 weeks. Documentation of vCR requires confirmation by biopsy of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy. In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response. Note that in the study, a biopsy for confirmation of CR is not mandatory but highly recommended.
- Partial response of externally visible disease (vPR): decrease of 50% (WHO criteria) or greater in the sum the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks
- Stable externally visible disease (vSD): not meeting criteria for vCR, vPR, or progressive disease

- Progression of visible disease (vPD): increase of ≥25% (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s)

New Lesions

A new cutaneous lesion consistent with CSCC will be considered as cPD if the lesion is ≥10 mm in both maximal perpendicular diameters and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with CSCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered CSCC and deemed cPD.

Overall Clinical Responses For All Possible Combinations of Clinical Tumor Responses For Locally Advanced CSCC

Externally Visible Tumor Dimension[a]	New Lesions[a]	Clinical Response
vCR	No	cCR[b]
vPR	No	cPR[c]
vSD	No	cSD[d]
vPD	Yes or No	cPD[e]
Any	Yes	cPD

a See above for definitions
b Clinical Complete Response
c Clinical Partial Response
d Clinical Stable Disease
e Clinical Progression of Disease

Composite Response Criteria: For patients who have disease that is measurable by BOTH clinical response criteria by digital medical photography and RECIST 1.1 using radiologic imaging.

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
cCR	CR	cCR
cCR	PR or SD	PR
cPR	CR, PR, or SD	PR
cSD	CR or PR	PR
SD	SD	SD
PD	Any	PD
Any	PD	PD

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to SAR444245 and/or cemiplimab, the Sponsor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the Sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

10.11 APPENDIX 11: GUIDELINES FOR BIOPSIES OF LOCALLY ADVANCED CSCC FOR ASSESSMENT OF OBJECTIVE RESPONSE OR FOR INDETERMINATE-APPARENT LESIONS

This appendix provides guidance for biopsies in patients with locally advanced CSCC. Because of the potential for sampling error with any single biopsy, two separate sites (preferably on the same target lesion) should be biopsied for any biopsy assessment.

Note that biopsies for biomarkers and pharmacodynamic exploratory purposes are addressed in the Laboratory Manual.

Timepoints:

- Baseline or at any scheduled response assessment (not mandatory, will be performed if needed to differentiate benign versus malignant area of skin):

  Areas of indeterminate-appearing tissue should be biopsied to distinguish malignant tissue versus benign process (eg, scarring, fibrosis). In circumstances in which biopsies are planned, it is preferred that these be performed on the day of a regularly-scheduled response assessment.

- At clinical complete response (not mandatory): Complete response status for externally visible lesions requires biopsies of 2 sites on the same lesion which are histologically negative for malignancy.

Research procedures for ALL biopsies:

1. Where and How:

   The technique and sites of biopsies will be selected by the investigator based on the sizes and locations of lesions. Generally, biopsies will be 3 to 5 mm punches. Biopsies should not be taken at the perimeter of a lesion because this could interfere with measurement of bi-dimensional perpendicular diameters for response assessments. Whenever possible, biopsy sites should be ≥5 mm from the edge of baseline lesional area.

   For indeterminate-appearing tissue: Biopsies should be taken at baseline and at any response assessment if there is tissue that is indeterminate-appearing regarding presence of benign versus malignant tissue. When the decision is made to biopsy a lesion (or an area of a lesion) to clarify benign versus malignant status, it is recommended to obtain 2 biopsies from 2 sites (1 from each site), to be sent for local pathology review). Pathology reports will be sent for central review.

2. Annotation and Photography

   The punch biopsies should be labeled (annotated) on the patient and photographed, such that on review of the photograph the following information is clear for each biopsy site: the study week and day of the biopsy (eg, Baseline, when relevant for distinguishing benign from malignant or Cycle X, Day Y), the identifying number of the biopsy (because at least 2 sites would be biopsied), and which samples are for central review and which samples are for local review. The tumor will also be annotated with a skin pen to indicate

the tumor perimeter and delimiters of the longest bi-dimensional perpendicular axes. All biopsies will be photographed and annotated.

Annotated photographs must be uploaded into the secured system indicated by the Sponsor (see Appendix 12 [Section 10.12]).

For each site that is biopsied to clarify indeterminate tissue, the entire block for one biopsy sample (designated for central) must be submitted to the vendor as per the Central Laboratory Manual. Because each biopsy site is sampled twice (closely adjacent samples) when there is indeterminate-appearing tissue, the second sample may be used for local pathology review. If only 1 adequate (eg, interpretable by pathologist) sample is obtained at a biopsy site, it will be provided to the Sponsor for potential central review to address the study objectives.

3. Classification of Pathology Samples

   For response assessments in which biopsies were performed, pathology results guide the determination of the area of invasive CSCC versus benign tissue. Residual squamous carcinoma in situ will not be deemed to be invasive cancer. A minute focus of residual CSCC in an otherwise benign responding biopsy sample will not automatically supersede a determination of partial response. However, the best response that can be recorded if the pathology report demonstrates any residual CSCC is partial response (not complete response).

10.12 APPENDIX 12: MEDICAL PHOTOGRAPHS PROCEDURES

Image Capture

- Close-up view with millimeter scale of the target area of the CSCC
- Global view of the target CSCC area

The supplied equipment is to be used exclusively for this study. Details are included in the photography manual. All supplied photographic equipment remains the property of the Sponsor.

10.13 APPENDIX 13: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNAMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol-mandated procedures, screening and enrollment of participants and administration of study intervention may be temporarily delayed (see also Section 7.1.2).

10.13.1 Informed consent

The participant or their legally authorized representative (if allowed by local regulations) should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

10.13.2 Study procedures

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. If onsite visits are possible and there is a need to reduce the time spent on site to a minimum, the focus should be on IMP infusion/administration, collection of safety information (vital signs, adverse events) and safety blood collection (mainly biochemistry, hematology and ADA, if planned for the visit). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints, namely CT/MRI scan, digital medical photographs, and tumor tissue collection for this study.

If onsite visits are not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

- Remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data
- Visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely
- Use of local clinic or laboratory locations may be allowed

10.13.3 Statistical analysis

The impact of any regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.13.4 Temporary discontinuation

Study intervention must be administered intravenously and at study site under the responsibility of the Investigator. Consequently, for participants who have started treatment but are unable to come to the site, administration of study intervention must be paused until regular study visits can be safely resumed at the study site.

In the event of disruption of the clinical trial due to an epidemic/pandemic (eg COVID-19), reinitiation of IMP can only occur once the Investigator has determined, according to his/her best

judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

Contingencies implemented due to emergency will be documented.

10.14 APPENDIX 14: RISK ASSESSMENT

The information shown in Table 12 reflects the clinical safety data currently available in SAR444245 IB. For cemiplimab, the information below is per currently available USPI and EU SmPC. Please always refer to the latest version of the SAR444245 IB and cemiplimab local label for the most up-to-date safety data.

Table 12 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Infusion-related reactions	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the THOR-707-101/HAMMER study have reported such AE as detailed in the SAR444245 IB. Cemiplimab Common. The most common symptoms of infusion-related reaction were nausea, pyrexia, vomiting, abdominal pain, chills, and flushing.	SAR444245 Standard pre-medication Dose modification and treatment guidelines for SAR444245 infusion-related reactions are provided in Table 4. Cemiplimab Treatment guidelines for cemiplimab infusion-related reactions are provided in Table 4.
Hypersensitivity, including anaphylaxis	SAR444245 Not observed in non-clinical toxicology studies. No reports of anaphylaxis in the HAMMER study to date. Cemiplimab Not reported.	Exclusion of participants with known hypersensitivity or contraindication for the use of any component of SAR444245, PEG, pegylated drugs or cemiplimab
Infections	SAR444245 Nonclinical data do not indicate higher risk for infections. Adverse events of infections have been reported in the HAMMER study and are presented in the SAR444245 IB. Cemiplimab The most common Grade 3-4 infections (≥2%) were cellulitis, sepsis, pneumonia, skin infection, urinary tract infection.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Signs and symptoms of infection are monitored as part of TEAE.
Cytokine release syndrome	SAR444245 No major increases in cytokines have been reported in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported high grade CRS as detailed in the SAR444245 IB.	Study to be conducted at sites experienced with CRS management, with bed available in ICU. Premedication with paracetamol, diphenhydramine, ondansetron (or equivalent medications). Hydration guidelines, including management of anti-hypertensive

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Cemiplimab Not specifically reported.	treatment around the time of infusion, are provided. Extensive post-dosing monitoring will be performed. Dose modification and treatment guidelines for CRS are provided in Table 5.
Capillary leak syndrome (CLS)/Vascular leak syndrome (VLS)	SAR444245 Not observed in non-clinical toxicology studies. None reported in the HAMMER study.	Intensive monitoring in C1D1 and beyond in the first cycle. Participants are monitored for signs and symptoms of VLS. Dose modification and treatment guidelines for VLS are provided in Table 8.
Hematological/bone marrow toxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, SAR444245-related changes in clinical pathology parameters were observed at all doses and were generally most prominent 3 days following each dose. Changes in hematology parameters included decreased or attenuated reticulocytes followed by decreases in red blood cell (RBC) mass at [redacted] mg/kg/dose, and increased WBCs (lymphocytes and monocytes) and transiently mildly decreased platelets at [redacted] mg/kg/dose. The increases in lymphocytes were attributed to the expected pharmacology of SAR444245 and correlated with the gross and microscopic findings of splenic and lymph node enlargement and increased lymphoid cellularity; there were no microscopic or clinical correlates for the decreases in platelets. Adverse events of bone marrow toxicity have been reported in the HAMMER study and are presented in the SAR444245 IB.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Dose modification/discontinuation of IMP for Grade 3/4 anemia, thrombocytopenia and/or neutropenia as per general guidelines for the management of TRAEs (see Section 6.6.3).
Hepatotoxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in mice, males at [redacted] mg/kg/dose and females at [redacted] and [redacted] mg/kg/dose also had mild increases in AST and ALT activity that corresponded to a spectrum of microscopic findings in the liver including mononuclear cell infiltration, apoptosis, necrosis, mixed leukocyte inflammation, oval cell hyperplasia, and Kupffer cell hypertrophy. No such data are reported in 28-day Repeat-Dose Study of IV SAR444245 in non-human primates. A minority of patients in the HAMMER study have reported such AE as detailed in the IB. Cemiplimab Increase in liver enzymes is common. Grade 3-4 increased AST, INR and hypoalbuminemia were	Patients with significant impaired liver functions are excluded. Monitor clinical signs and symptoms of hepatic impairment as part of TEAE. Monitor liver function parameters (AST, ALT, bilirubin & ALP) regularly from screening and throughout the study. Dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Table 6.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	reported in 3%, 2%, and 1% of participants in clinical trials, respectively.	
Nephrotoxicity	SAR444245 There are no non-clinical data indicating a potential for nephrotoxicity. One relevant serious adverse event (SAE) considered related to SAR444245 (Acute Kidney Injury) has been reported in the HAMMER study within a monotherapy cohort. Investigator's assessment is that it is related to the CRS occurring in the same patient. Sponsor's assessment was that the kidney injury was related to increased fluid losses from persistent fever. Cemiplimab Nephritis is uncommon (under immune-related reactions).	Participants must have appropriate eGFR to be included. Monitor renal function parameters (BUN/urea & creatinine) regularly from screening and throughout the study. Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 6.
Neurological AEs, ICANS	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported such AE as detailed in the IB. One SAE of CRS (Grade 4 with 24 µg/kg monotherapy) associated with neurological manifestations [hypertension, chills/rigors, flushing, fever (maximum temperature: 102.8 F), as well as neurological symptomatology (loss of ability to follow commands, confusion, aphasia, and involuntary fist clinching)] was reported in the HAMMER study. The event resolved completely within 30 to 60 mins after treatment with tocilizumab and steroid. This patient later discontinued the study. Cemiplimab Described under immune-mediated adverse events. US label: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy. Uncommon in the EU SmPC: meningitis (Grade 4), paraneoplastic encephalomyelitis (Grade 5), Guillain-Barre syndrome, central nervous system inflammation, chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, neuropathy peripheral.	Exclusion of participants with: active brain metastases or leptomeningeal metastases. See E 06 for details. Guidelines for the management of ICANS are provided in Table 7.
Cardiovascular effects, including QT interval prolongation	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, there were no SAR444245-related changes to the PR or QRS intervals or the heart rate (HR) corrected QTca interval. There was a SAR444245-related, dose dependent, non-adverse higher HR at doses of [redacted] mg/kg/dose beginning on Day 1 compared to the control dose group and	Routine mitigation: Selection of qualified investigative centers with availability of intensive critical care/equipment. Exclusion of patients with severe or unstable cardiac condition within 6 months prior to starting study treatment. See E 13 for details.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	persisting through each respective dose following applicable telemetry recording sessions, with recovery. There was also an expected physiologic inverse relationship in the respiration rate (RR) intervals as well as the raw QT intervals, which correlated to the changes in HR, and were also considered to be non-adverse. There were increases in individual females of troponin I minimal post first dose. There were marked decreases in females and males. These changes correlated with findings of mononuclear cell infiltrates and/or myocardial degeneration. All changes however, recovered by the end of a 28 day or 42/44 day treatment free period. A minority of patients in the HAMMER study have reported such AE as detailed in IB. Cemiplimab Uncommon: myocarditis (including autoimmune myocarditis), pericarditis. Vasculitides also reported.	ECG, LVEF, and vital sign monitoring and coagulation tests performed at screening and thereafter as clinically indicated. Blood pressure and vital signs monitored closely during the 24-hour hospitalization for C1 and C2. For subsequent cycles, monitoring will depend on site assessment of participant's symptoms.
Immune-mediated Adverse Events	SAR444245 A minority of patients in the HAMMER study have reported such AE as detailed in the IB. Cemiplimab Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated dermatologic events including erythema multiforme and pemphigoid, SJS and TEN. Other reactions: - Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a VogtKoyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss. - Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis. - Musculoskeletal and Connective Tissue: Myositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica. - Hematological and Immunological: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection. Cardiovascular, renal, and neurological reported in the respective sections.	Exclusion of participants with: Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). Close monitoring for endocrine abnormalities and other potentially autoimmune phenomena will be performed. Dose modification and treatment guidelines for immune-related reactions are provided in Table 6.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	SAR444245 No studies have been conducted with SAR444245 on fertility or general reproductive performance. Cemiplimab Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. If a woman chooses to be treated with cemiplimab, she should be instructed not to breast-feed while being treated with cemiplimab and for at least 4 months after the last dose.	Exclusion of participants who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, as per inclusion criterion I 08. Guidance on highly effective contraceptive methods is provided in the protocol. Pregnancy tests are to be performed regularly as described in Section 8.2.5.
Use in children	The safety and efficacy of the study interventions in children below 18 years of age have not yet been established.	Exclusion of participants under 18 years of age.
Participants over 75 years of age	SAR444245 At this stage of development, no safety data are available for this population. Cemiplimab Of the 163 patients with metastatic and locally advanced CSCC who received LIBTAYO in clinical studies, 72% were 65 years or older and 37% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.	No specific mitigation strategy for this population.
Clinically significant medication errors	With the increased complexity of the design of oncology clinical trials, medication errors need to be considered. Although their occurrence is estimated to be low (eg, chemotherapy errors occur at a rate of about one to four per 1000 orders), their impact may be high. According to the report on medication safety in cancer clinical trials, the processes in which the errors originated were prescribing (47%), administering (10%), dispensing (6%), and monitoring (5%). Prescribing errors typically arise from not following an institutional procedure or the protocol (39%, most likely due to the protocol procedures differing from existing standards of care), followed by the written order (30%), and poor communication involving both the healthcare team and the patient (26%) (48, 49, 50).	Strict adherence to the protocol. Adequate and verified training of staff at investigational sites.
Overdose and its treatment	There is no specific antidote for overdose with SAR444245. No specific information is available on the treatment of overdose of cemiplimab.	Strict adherence to the protocol. Adequate and verified training of staff at investigational sites. See Section 6.8.
Study procedures Biopsies of (potentially) tumor tissue are expected during the trial.		Strict adherence to the guidance in the protocol

10.15 APPENDIX 15: ASTCT ASSESSMENT FOR ICANS AND CRS

Table 13 - Encephalopathy assessment ICE tool for ICANS grading

Immune Effector Cell-Associated Encephalopathy (ICE) assessment	Number of points
Orientation: Orientation to year, month, city, hospital	4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1 point
Attention: ability to count backwards from 100 by 10	1 point

Source: (2).

Table 14 - ASTCT ICANS consensus grading for adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unrousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

a A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unrousable.

b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medications).

c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v 5.0, but they do not influence ICANS grading.

d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v 5.0.

Abbreviations: ASCT=American Society for Transplantation and Cellular Therapy; CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune Effector Cell-Associated Encephalopathy; ICP=intracranial pressure; N/A=not applicable.

Source: (2).

Table 15 - ASTCT CRS consensus grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
			With	
Hypotension[b]	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or[b]	
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v 5.0 but they do not influence CRS grading.

a Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Abbreviations: ASCT=American Society for Transplantation and Cellular Therapy; BiPAP=Bi-level positive airway pressure CPAP= Continuous Positive Airway Pressure; CRS=Cytokine release syndrome.

Source: (2).

10.16 APPENDIX 16: ABBREVIATIONS

1L: first-line
ADA: anti-drug antibody
AESI: adverse event of special interest
ANSM: National Agency for the Safety of Medicines and Health Products
ART: anti-retroviral therapy
ASTCT: American Society for Transplantation and Cellular Therapy
BfArM: German Federal Institute for Drugs and Medical Devices
BOR: best overall response
CBR: clinical benefit rate
CI: confidence interval
CLS: capillary leak syndrome
COVID-19: coronavirus disease 2019
CR: complete response
CRF: case report form
CRR: complete response rate
CRS: cytokine release syndrome
CSCC: cutaneous squamous cell carcinoma
CSF: colony-stimulating factor
CT: computed tomography

[redacted]

CTLA-4:	cytotoxic T-lymphocyte-associated protein 4
CyTOF:	mass cytometry time of flight

[redacted]

DLT:	dose-limiting toxicity
DMC:	Data Monitoring Committee
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
EOT:	end of treatment
FU:	follow-up
HPRA:	Health Products Regulatory Authority
IB:	Investigator's Brochure
ICANS:	immune effector cell-associated neurotoxicity syndrome
ICF:	Informed Consent Form
ICI:	immune checkpoint inhibitor
IHC:	immunohistochemistry
IL:	interleukin
ILC-2:	innate lymphoid cell
IMP:	investigational medicinal product
irAE:	immune-related adverse event
IRR:	infusion-related reaction
IV:	intravenous
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
mTPI2:	modified toxicity probability interval 2
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP:	non-human primate
ORR:	objective response rate

[redacted]

OTC:	over-the-counter
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease
PD1:	programmed cell death protein 1
PD-L1:	programmed cell death-ligand 1
PDy:	pharmacodynamic
PFS:	progression free survival
PK:	pharmacokinetic
PR:	partial response
PT:	preferred term
Q2W:	every 2 weeks
Q3W:	every 3 weeks
RECIST:	response evaluation criteria in solid tumor
RP2D:	recommended Phase 2 dose
SARS-CoV-2:	Severe acute respiratory sundrome coronavirus 2
SB:	Study Board

SD:	stable disease
SOC:	system organ class, standard of care
SpO2:	oxygen saturation
TEAE:	treatment-emergent adverse event
TEN:	toxic epidermal necrolysis
TLS:	tumor lysis syndrome
TRAE:	treatment-related adverse event
TTR:	time to response
UK:	United Kingdom
VLS:	vascular leak syndrome
WHO:	World Health Organization

10.17 APPENDIX 17: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amended protocol 01 (19 March 2021)

This amended protocol 01 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for the amendment is to clarify criteria for cytokine release syndrome reporting.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Footnote J has been updated to add that CRS will be graded using ASTCT criteria integrated with central laboratory cytokine results.	To clarify CRS grading criteria for reporting
1.4 Biomarker flowchart	Clarified that every effort should be made to obtain a cytokine sample for an event of CRS of any grade.	To facilitate comprehensive CRS reporting
6.6.4.3 Fever, flu-like symptoms, and cytokine-release syndrome (CRS)	Clarified that central laboratory cytokine results will be integrated into the grading of CRS events and the guidelines provided are for any suspected CRS event.	To facilitate comprehensive CRS reporting

Amended protocol 02 (04 May 2021)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for the amendment is to respond to the Health Authority (Food and Drug Administration, [FDA]) requests, including revision of study design to include a dose escalation.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and relevant sections of the protocol (Sections 4, 6 and 9)	Initial safety run-in part replaced by dose escalation with SAR444245 starting dose of 16 µg/kg (DL1) to determine the recommended Phase 2 dose (RP2D) in combination with cemiplimab. Due to these modifications the study design has changed from Phase 2 to Phase 1/2.	Regulatory Authority (FDA) request
1.1 Synopsis and 6.1.2.1 Premedication for SAR444245	Details on decision criteria to stop SAR444245 premedication after cycle 4 have been added.	Regulatory Authority (FDA) request
1.3 Schedule of activities (SoA)	Footnote K has been updated.	To clarify and be in alignment with exclusion criterion E06
1.4 Biomarker flowchart	The following text has been added: [redacted]	To have the sample drawn from patients enrolled in RP2D
1.5 Pharmacokinetic flowchart	Footnote A related to ADA sampling has been removed.	Regulatory Authority (FDA) request
4.1 Overall design	The following DLT criteria have been updated as follows: "Grade 4 neutropenia for ≥7 consecutive days" updated to "Any Grade 4 neutropenia irrespective of duration" "Grade 3 or 4 neutropenia complicated by fever (temperature of >38.3°C [101°F] or a sustained temperature of ≥38.0°C [100.4°F] for more than 1 hour) or microbiologically or radiographically documented infection" replaced by "Any febrile neutropenia" "Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention" updated to "Grade 3 thrombocytopenia associated with transfusion in addition to bleeding and any Grade 4 thrombocytopenia" "Grade 3 or above ALT or AST in combination with a bilirubin >2 times ULN with no evidence of cholestasis or another cause such as viral infection or other drugs" updated to "Grade 3 or above ALT and AST increase" The following DLT criterion has been added: "Grade 4 laboratory abnormalities" The following DLT criterion has been removed: "The following non-hematologic AEs are exceptions: Grade 3 or 4 laboratory abnormalities that are not clinically significant per recruiting Investigator and Sponsor"	Regulatory Authority (FDA) request
	Specified that in the event of an excessive toxicity any cohort can be stopped as per Study Committee and Sponsor decision	Regulatory Authority (FDA) request

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	E14 updated to allow individuals with ≤Grade 1 peripheral neuropathy instead of Grade 2. E36 "Aspartate aminotransferase and/or alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases)" updated to "Aspartate aminotransferase and alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases)"	Regulatory Authority (FDA) request
8.2.2 Vital signs	Collection of vital signs including timing and in/out-patient settings has been clarified for participants in dose escalation and other participants at Cycle 1 and beyond. The following text has been added: "From Cycle 2 and beyond study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, 4 to 6 hours post-dose, or as clinically indicated".	Regulatory Authority (FDA) request
8.7 Biomarkers	The following text has been added: "[redacted]	To have the sample drawn from patients enrolled in RP2D
10.3.3 Recording and follow-up of AE and/or SAE	The following text has been added to further clarify assessment of causality: The Investigator should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment SAR444245, cemiplimab or the combination.	Regulatory Authority (FDA) request
All Sections	Minor editorial and document formatting revisions	Minor corrections for consistency

Amended protocol 03 (25 August 2021)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

In response to requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Irish (Health Products Regulatory Authority [HPRA]), and German (Federal Institute for Drugs and Medical Devices [BfArM]) Health Authorities after initial review, the protocol is being amended to correspond with the responses previously provided. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Protocol title	"(Pegasus Skin 201)" has been added to protocol title	Harmonization per program level approach
1.1 Synopsis, 3 Objectives and Endpoints, 9.4.3 Secondary endpoint(s)	Definitions of Time to complete response, Time to response, and Duration of response have been revised as follows: • Time to CR defined as the time from the first administration of 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 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 RECIST1.1 or modified WHO criteria or composite criteria, whichever relevant. • Duration of Response 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 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.	For clarification
1.1 Synopsis Figure 1 1.3 Schedule of Activities (SoA) 4.1 Overall Design 6.1.1 Investigational medicinal product 9.5 Interim analysis	"Study Committee" has been replaced by "Study Board" and its description in Section 4.1 updated as follows: "The study Investigators (or designee) participating in the dose escalation part of the trial and the Sponsor clinical team members will constitute the Study Board (SB). The SB will meet first when the first patient is treated in the dose escalation part and will review clinical data of each individual patient treated in the dose escalation part on a regular basis, in order to adjust the number of patients to be enrolled and to decide dose confirmation, dose reduction, dose escalation as appropriate on the basis of their knowledge of the safety data. Minutes of each meeting will be written by the Sponsor and distributed to all sites participating in the dose escalation. Decisions regarding final dose selection will be made during one of the study board meeting and documented in the meeting minutes.".	Harmonization per Sanofi standard terminology
1.1 Synopsis 4.1 Overall Design	Observation and Follow-up period have been revised as follows: • Under the definition of End of Treatment and Follow-up for participants who discontinue study treatment without radiological or clinical PD or who complete 35 cycles of treatment without PD, "final" has been added to cohort cut-off • Under the definition of End of Treatment and Follow-up for participants who discontinue study treatment with radiological or clinical PD (per RECIST 1.1 or modified WHO Criteria for medical photographs) or [redacted] the following text "or until start of another anticancer	For clarification

Section # and Name	Description of Change	Brief Rationale
	therapy or cohort cut-off, whichever comes first" has been removed • Under the definition of Survival Phone Call Follow-Up Period the following text "or until the last participant to enter Survival Follow-Up has been followed for no more than 3 years" has been replaced by "final cohort cut-off"	
9.5 Interim Analyses	The study cut-off date has been replaced by cohort cut off for final analysis.	
1.1 Synopsis 4.1 Overall Design 9.3 Populations for Analyses	The definition of DLT-evaluable participants has been updated to "all participants in the dose escalation who have been treated and observed for at least 21 days".	Harmonization per program level approach
1.1 Synopsis	"Independent" has been removed before "Data Monitoring Committee" and "No" has been replaced with "Yes".	DMC remains independent. Harmonization per Sanofi standard terminology
1.3 Schedule of Activities (SoA)	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	Regulatory Authorities (ANSM and HPRA) request
8 Study Assessments and Procedures	The following text has been added: "A comprehensive medical history will be assessed for any cardiovascular signs or symptoms prior to treatment, along with a baseline ECG, echocardiogram and troponin level".	
8.2.3 Electrocardiograms and LVEF	Troponin has been added as an example of cardiac enzymes within additional evaluation to carry out when clinically indicated.	Regulatory Authorities (ANSM, BfArM and HPRA) request
	The following text has also been added for evaluations during treatment and post treatment follow-up: "In case of a suspicion of a drug related cardiac event (eg, including signs/symptoms of cardiac disease, ECG and/or echo changes, cardiac troponin elevation, etc.) Investigators are encouraged to do ECG, echocardiography and/or cardiac biomarker tests, as medically indicated, including cardiology consultation".	Regulatory Authorities (ANSM and HPRA) request
10.2 Clinical laboratory tests	Troponin has been added to other screening tests.	Regulatory Authorities (ANSM and HPRA) request
1.4 Biomarker Flowchart	Sample collections for participants enrolled in the dose escalation dose 16 µg/kg and dose 24 µg/kg have been specified.	For clarification
5.1 Inclusion Criteria	In I06, provision of tumor tissue, collection at screening and on-treatment for participants in dose 16 µg/kg and dose 24 µg/kg have been specified.	
8.7 Biomarkers	The following text has been removed: [redacted]	

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Following decision to set up a DMC the text following text "Study Committee and Sponsor can decide to stop any cohort in case excessive toxicity (for example but not limited to excessive ir-AE or excessive number of G4/5 events) is observed" has been revised as: "Study Board (during dose escalation), Data Monitoring Committee (DMC) (during dose expansion) and Sponsor can decide to stop any cohort in case excessive toxicity (for example but not limited to excessive ir-AE or excessive number of G4/5 events) is observed".	Regulatory Authorities (ANSM, HPRA and BfArM) request
9.5 Interim analyses	The following text has been added: "After the dose is confirmed by the SB the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the DMC. The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. DMC will review safety data periodically. Ad hoc DMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other SAR444245 studies. The DMC procedures will be detailed in the DMC charter and approved by the DMC members".	
10.1.5 Committee structure	The description of the DMC has been added.	
4.1 Overall Design	The following text has been added: "After dose escalation, occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants per regimen will trigger SB to rapidly convene to assess safety or need to pause enrollment to allow for a safety review".	Regulatory Authority (ANSM) request
4.3 Justification for Dose	Updated based on most recent data.	To include the most recent dose justification
5.1 Inclusion Criteria	In I06 "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment"	Harmonization per program level approach
5.1 Inclusion Criteria 10.7 Appendix 7: Country-Specific Requirements	I02 has been updated with the following country specific requirements: - Cohort A will not be open in Ireland - In France participants with BRAF-mutant melanoma will not be included in Cohort A	Regulatory Authorities requests (HPRA and ANSM, respectively)
5.2 Exclusion Criteria	E07 "History of allogenic or solid organ transplant" has been revised to "History of allogenic tissue/solid organ transplant". E20 "Known hypersensitivity to or contraindication for the use of SAR444245, PEG, pegylated drugs, cemiplimab, and SAR444245 premedication (acetaminophen, diphenhydramine [or cetirizine, promethazine, dexchlorpheniramine], ondansetron [or granisetron, dolasetron, tropisetron, palonosetron])" has been revised to "Known hypersensitivity to or contraindication for the use of any study intervention including premedication to be administered in this study, as well as PEG or any pegylated drug".	Harmonization per program level approach Regulatory Authority (BfArM) request

Section # and Name	Description of Change	Brief Rationale
6.6 Dose modification	In subsections 6.6.1 and 6.6.2, dose omission has been removed and replaced by cycle delay when relevant. In subsections 6.6.2 and 6.6.3 the following text regarding the treatment resumption after cycle delay and treatment withhold has been deleted: “or is stable and manageable through supportive/medical therapy”.	As per protocol if one drug is held then other drug will also be held, so this will constitute cycle delay
	In subsection 6.6.3 (General guidelines for the management of treatment-related adverse events) the following text has been added: “Study intervention should be held in case of significant cardiac event (if possible, confirmed by a cardiologist) or suspicion of an immune-mediated myocarditis until this has been assessed for a relationship to SAR444245 or cemiplimab”.	Regulatory Authorities (ANSM and HPRA) request
	In Table 6 the guidelines for the management of immune-related hepatitis have been revised to separate management of Grade 2 and Grade ≥3 hepatitis.	Regulatory Authority (ANSM) request
8.2.2 Vital signs	The requirement to measure vital signs in a semi-supine position has been removed.	Harmonization per program level approach
7.1.1 Permanent discontinuation 8.3 Adverse events (AEs), Serious adverse events (SAEs) and other safety reporting 10.1.3 Informed consent process 10.13.1 Informed consent	“If allowed by local regulations” has been added after “legally authorized representative” to cover for country-specific regulations.	Regulatory Authority (BfArM) request
8.10 Use of biological samples and data for future research	The following text: “Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples)” has been deleted. Duration of biological sample storage has been updated to “up to 25 years”.	Harmonization per Sanofi standard terminology
9.3 Populations for Analyses	The definition of efficacy population has been revised to “Efficacy population will include all participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment”.	To characterize efficacy excluding participants newly enrolled
9.4.1 General considerations	“By dose (as applicable)” has been added to efficacy analyses.	For clarification
9.4.3 Secondary endpoint(s) 9.4.5 Other safety analyse(s)	“When relevant” has been added before “for laboratory variables” in Section 9.4.3.8 and before “the summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs” in Section 9.4.5, respectively.	These analyses will be done as needed following analyses of abnormalities according to NCI-CTCAE grade
9.4.5 Other safety analyse(s)	“ECG” has been removed from quantitative analyses	Harmonization per program level approach

Section # and Name	Description of Change	Brief Rationale
10.1.9 Study and site start and closure	The following paragraph has been added: "If the cohort/study is early terminated the patients who are receiving and benefitting from study treatment as per Investigator judgment may continue study treatment until protocol defined treatment discontinuation criteria are met. The patients who continue study treatment after early study termination should be followed for safety (ie, study treatment administrations, ongoing SAE/related AE, new related AE, AESI or SAE and their associated concomitant medications and lab if any) and end of treatment reason during this time period."	For clarification
10.8 Appendix 8: Response evaluation criteria in solid tumors (RECIST) 1.1	"Or progressive disease" has been removed from the sentence "Confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response or progressive disease".	Typographical error
10.14 Appendix 14: Risk assessment	The following text has been added to clarify the source of information for Table 12: "For cemiplimab, the information below is per currently available USPI and EU SmPC" Reference to cemiplimab local label for up-to-date safety data has also been added.	For clarification
Throughout the document	Minor editorial updates.	For consistency and clarification

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