AMENDED CLINICAL TRIAL MASTER PROTOCOL 02

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with advanced and metastatic gastrointestinal cancer**
Protocol number:	**ACT16902 Master**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with other anticancer therapies for the treatment of participants with gastrointestinal cancer (Master protocol)**
Acronym	**Pegathor Gastrointestinal 203**
Study phase:	**Phase 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):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Master Protocol 02	All	21 January 2022, version 1 (electronic 4.0)
Amended Clinical Trial Master Protocol 01	All	30 August 2021, version 1 (electronic 2.0)
Clinical Trial Master Protocol		20 July 2021, version 1 (electronic 1.0)

Amended protocol 02 (21 January 2022)

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 main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Belgian, Italian, German (Federal Institute for Drugs and Medical Devices [BfArM]), and South Korean Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page and 1.1 Synopsis	The following study name: "Pegasus Gastrointestinal 203" has been removed from the protocol title and the new study acronym "Pegathor Gastrointestinal 203" has been added on the cover page.	For consistency across the program.
1.1 Synopsis, 3 Objectives and Endpoints, and 9.4.3 Secondary endpoint(s)	Definitions of Time to response and Duration of response have been revised as follows: • Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or	For clarification.

Section # and Name	Description of Change	Brief Rationale
	CR that is subsequently confirmed and determined by Investigator per RECIST 1.1. • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first.	
1.1 Synopsis and 6.1.2 Non-investigational medicinal products	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.
1.1 Synopsis, 6.1.2 Non-investigational medicinal products, and 10.10 Appendix 12: Table 8 Risk assessment	Antiemetic SAR444245 premedication with ondansetron or equivalent has been removed.	Antiemetic is removed from premedication list based on new tolerability data from the first-in-human study.
1.1 Synopsis and 9.4.3.5 Adverse events	Treatment-related TEAEs will be analyzed overall, regardless of the drug	To assess treatment-related AE of the regimen as whole (SAR444245 with other anticancer therapies).
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.	To allow assessment of any potential cardiotoxity.
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, echocardiography and troponin level”.	
8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)	Troponin has been added as an example of cardiac enzymes within additional evaluation to carry out when clinically indicated. The following text has also been added for evaluations during treatment and post treatment follow-up: “During treatment, or post treatment follow-up: Troponin will be performed at Cycle 4 Day 1. 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”.	

Section # and Name	Description of Change	Brief Rationale
10.2 Clinical laboratory tests	Troponin has been added to “other screening tests”.	
1.3 Schedule of Activities (SoA)	Footnote h “For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.7).” has been added. The numbering of the remaining footnotes has been updated. “and microscopic examination (if blood or protein is abnormal)” has been added for footnote i for urinalysis. “Tumor biopsy during treatment period should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous” has been removed from footnote l.	For consistency and clarity.
1.4 Biomarker flowchart, 6.1.4 Readiness for treatment of severe cytokine release syndrome	The following statement “alternative therapies per site practice in CRS management” has been added to “tocilizumab”.	For flexibility following an issue with tocilizumab availability.
1.4 Biomarker flowchart	The following sentence has been added for footnote f “If there is not a baseline biopsy, an on-treatment biopsy is not needed or recommended”.	For clarity.
1.5 Pharmacokinetic flowcharts	In Section 1.5.1, 'D2','D3','D4' are removed and replaced by D1 within the line 'Day' at Cycles 1 and 4. In Section 1.5.2, footnote c “PK sample can be collected at any time during the second day of the cycle” is added to PK sample collection at 24h.	For consistency and clarity.
5.1 Inclusion Criteria, 8.2.5 Pregnancy testing, 8.3.5 Pregnancy, and 10.2 Clinical laboratory tests	In I03, the requirement for contraception for male participants has been changed from “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” to “at least 3 days [corresponding to time needed to eliminate SAR444245] after the last dose of SAR444245”.	To change measures for male participants as per Clinical Trials Facilitation and Coordination Group (CTFG) guideline on recommendations related to contraception and pregnancy testing in clinical trials version 1.1 of 21 Sept 2020. As SAR444245 is not genotoxic, there is no need to extend the requirement for contraception to 90 days (3 months) for male participants, but to take into account the 5 half-lives of the study intervention before its elimination.
	The recommended duration for continuing contraception after last dose of study intervention has been changed for female participants in Cohorts A, B1, B2, B3, C, and D1 (SAR444245 plus pembrolizumab) from 180 days to 120 days, and 60 days for participants in Cohort D2, and the requirement of extension extra 30 days (1 month) has been removed.	None of the products in combination is genotoxic in this study, there is no need to extend the requirement for contraception to 30 days (1 month) corresponding to a menstrual cycle for female participants.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	E 18 has been changed from "Known hypersensitivity (≥ Grade 3) 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 (≥ Grade 3) 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 that patients with known hypersensitivity to any excipient of the study interventions and hypersensitivity to any E. Coli-derived protein must be excluded.
	E 23 has been changed from: "Participation in a concurrent clinical study in the treatment period" To "Current enrollment or past participation in a study of an investigational treatment or an investigational device within 28 days prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational treatment".	For clarification.
5.4 Screen Failures	The following text: "A participant may be rescreened only once" has been added.	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.	For correction. Direct-to-patient shipment of IMP is not possible in this study.
7.1.1 Permanent discontinuation, 8.3 Adverse events (AEs), Serious adverse events (SAEs) and other safety reporting, 10.1.3 Informed consent process, and 10.9.1 Informed consent process	"If allowed by local regulations" has been added after "legally authorized representative" to cover for country-specific regulations.	Regulatory Authority (BfArM) request.
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 has been removed. All AEs and SAEs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards.

Section # and Name	Description of Change	Brief Rationale
8.6 Biomarkers	[redacted] s been added for "This method will only apply to samples from clinical sites not exhibiting feasibility constrains on handling/shipment".	To improve flexibility in case local constrains exist.
8.6 Biomarkers	Concerning collection of samples, the following text "will be stored for a period of up to 15 years after the last participant's last visit for potential re-analyses" has been changed to "may be used for further research if consent is provided (see Section 8.9)".	Harmonization per Sanofi standard terminology.
8.9 Use of biological samples and data for future research and 10.5 Appendix 5: Genetics	The text was revised to state that the duration of storage for biological samples and relating data is up to 25 years. The duration of biological sample storage was previously given as a maximum of 15 years.	For consistency with the latest Sanofi standards.
9.3 Population of analyses	Update of Efficacy population definition	To characterize efficacy excluding participants newly enrolled.
9.4.3.2 Duration of response	Update the definition for DoR analysis.	For clarity.
9.5 Interim analysis	The following sentence has been added "Occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants will trigger ad hoc DMC."	For clarity.
10.2 Appendix 2: Clinical laboratory tests	The following footnote d: "Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during the Treatment period and as clinically indicated" has been added. The numbering of the remaining footnotes has been updated.	For clarification.
	For footnote f virus serology testing, hepatitis B and C tests at screening have been added.	Regulatory Authority request.
10.7 Appendix 7: Country-specific requirements	Country-specific requirements for Italy has been added.	Regulatory Authority request.
10.10 Appendix 10: Risk assessment	In Table 5, the row for drug-drug interactions has been deleted.	For consistency.
Throughout	Minor editorial updates	For consistency and clarification.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with advanced and metastatic gastrointestinal cancer

Brief title: A study of SAR444245 combined with other anticancer therapies for the treatment of participants with gastrointestinal cancer (Master protocol)

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.

The proposed study aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with other anticancer therapies will result in a significant increase in the percentage of patients experiencing an objective response in the setting of various advanced gastrointestinal cancers.

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals. This design is with the flexibility to open new treatment cohorts as new treatment combinations become available and close existing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity.

The information that is introductory and common to all cohorts is included in the present document ("Master Protocol"), and cohort-specific elements are included in separate substudies.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with other anticancer therapies	• 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)

Secondary	
• To assess the safety of SAR444245 in combination with other anticancer therapies	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (2)
• To assess other indicators of antitumor activity	• Time to response (TTR), defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1 • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first • Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months determined by Investigator per RECIST 1.1. • Progression-free survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by Investigator as per RECIST 1.1 or death due to any cause, whichever occurs first
• To assess the pharmacokinetics (PK) of SAR444245 in combination with other anticancer therapies	• Plasma concentrations and where applicable PK parameters of SAR444245
• To assess the immunogenicity of SAR444245	• Incidence of anti-drug antibodies (ADAs) against SAR444245

For China, please see Section 10.7 for details.

Overall design:

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with other anticancer therapies in participants with advanced or metastatic gastrointestinal cancer.

Brief summary:

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

Special considerations pertaining to methodology

Interactive Response Technology (IRT) will be used to control recruitment, assignment per site and to facilitate the handling, management, and accountability of drug supply.

Number of participants:

Please refer to the individual substudy for the numbers of participants to be enrolled and treated at the recommended safe dose.

Note: Enrolled participants are all participants from 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 adverse event (AE) or other full permanent discontinuation criteria as described in Section 7; or completion of Cycle 35 (if applicable).

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, whichever comes first. 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 PD** or who complete 35 cycles of treatment without PD will be followed every 3 months ±7 days from last IMP administration, for safety (as per Schedule of Activities [SoA]) and tumor imaging assessments 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 PD** will be followed for safety 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. Updated survival status may be requested by the Sponsor at any time during the study. Survival Phone Call Follow-up will continue until death, participant request to discontinue from follow-up, or cut-off date for the given cohort final analysis has been reached, or upon cancellation of Survival follow-up in the given cohort at the discretion of the Sponsor at any prior timepoint, whichever occurs first.

The cohort cut-off for the primary ORR endpoint analysis in each individual cohort is estimated to be approximately 9 months from the date of the last participant first infusion. This would allow the possibility to observe the response of the last participant for 6 months, assuming there is a response at first treatment assessment.

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 18 months from the corresponding cohort LPI. After this cut-off date for the final analysis, the participants of the given cohort still receiving study treatment in that specific cohort will be followed up as the cohorts after early termination described in Section 10.1.9.

Study intervention(s)

Investigational medicinal products

SAR444245

- **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**: IV infusion
- **Dose regimen**: 24 µg/kg administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle) for the treatment duration defined in the individual substudy.

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

See substudy protocols for other IMPs.

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 (PO) (or equivalent), and then optionally thereafter as needed.

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

SAR444245 premedication may be optional after 4 cycles

- For a participant who has no IRR during the first 4 cycles: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the participant experiences an IRR (any grade), 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 Cycle 5. If no IRR is observed during Cycle 5 without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during Cycle 5 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% confidence intervals (CIs) for ORR will be computed using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints:**
  - The time to response (TTR) will be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
  - The duration of response (DoR) will only be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
  - The clinical benefit rate (CBR) will be estimated by dividing the number of participants with clinical benefit by the number of participants in the efficacy population.
  - The progression free survival (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 Preferred Term (PT) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V 5.0 or American Society for Transplantation and Cellular Therapy (ASTCT) grade (all grades and Grade ≥3) for the exposed population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to permanent partial intervention discontinuation (any of the IMP components), TEAEs leading to permanent 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), participants who died by study period (treatment-emergent period,

post-treatment period) and reasons for death will be summarized. Immune Cell-Associated Neurotoxicity Syndrome (ICANS) and cytokine release syndrome (CRS) events will be graded using ASTCT Consensus Grading and will be summarized separately.

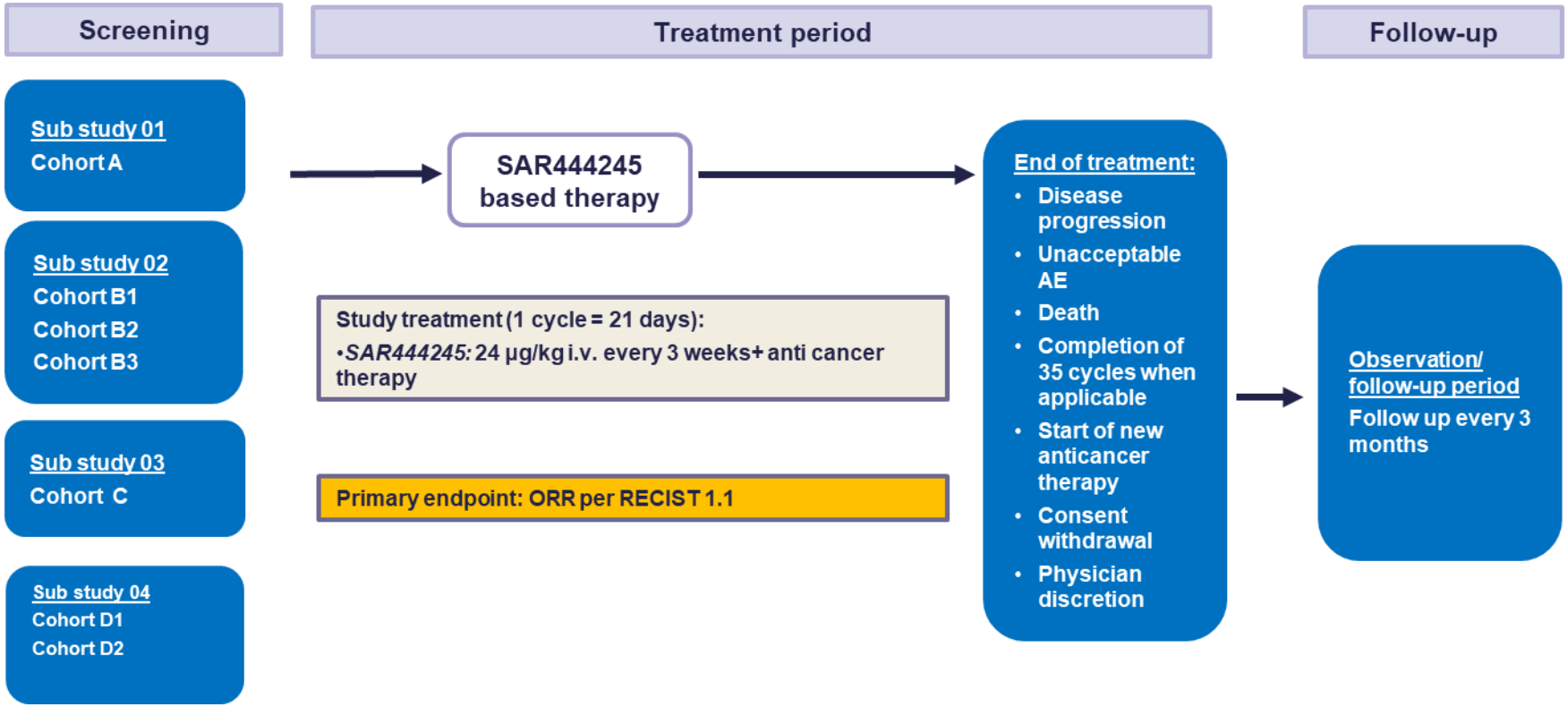
- Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V 5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period will be provided for the exposed population.

- **Analysis of other secondary endpoints:**
  - Plasma concentrations of each cohort by SAR444245 will be summarized with descriptive statistics. Where applicable, in addition PK parameters for SAR444245 will be summarized with descriptive statistics

Data Monitoring/Other Committee: Yes (see Section 10.1.5 for details)

1.2 SCHEMA

Figure 1 - Graphical study design



AE: adverse event; ORR: objective response rate; RECIST: Response Evaluation Criteria in Solid Tumors

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Informed consent	X										
Inclusion and exclusion criteria	X										
IRT contact	X	X			X	X					
Demography, medical/surgical and disease history	X										See Section 8
Body Weight / Height[g]	X	X	X	X	X	X	X				
Full physical examination	X					X					See Section 8.2.1
Directed Physical examination		X	X	X	X		X				See Section 8.2.1
Vital Signs	X	X	X	X	X	X	X				See Section 8.2.2
Performance status (ECOG)	X	X	X	X	X	X	X				
SpO_2	X	As clinically indicated									

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Laboratory and other investigations											
12-Lead ECG	X	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 (Cycle 4 Day 1)	As clinically indicated					See Section 8.2.3 and Section 10.2
Pregnancy test	X	X			X	X	X	X			See Section 8.2.5 and Section 10.2
Hepatitis serology, CD4 counts and viral load	X[h]	As clinically indicated									See Section 10.2 and Section 10.7
Hematology	X	X	X	X	X	X	X				See Section 10.2
Coagulation	X	As clinically indicated									See Section 10.2
Blood Chemistry	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 Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Urinalysis[i]	X	X			X	X	X				See Section 10.2
IMP											
SAR444245		X			X						
Hospitalization[j]		X									
AE/SAE assessment[k]	X	Continuously throughout treatment period					X				See Section 8.3
Prior/Concomitant Meds	X	Continuously throughout treatment period									See Section 6.8
First subsequent anti-cancer therapy						X	X	X	X	X	
Survival status										X	
Pharmacokinetic (PK) / Pharmacodynamic (PDy) / Immunogenicity assessments											
PK SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
ADA SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
PDy - Blood and tumor tissue collection[l,m]	See Biomarker Flowchart in Section 1.4										
Tumor assessment											
Brain imaging[n]	X										See Section 8.1
CT/MRI[o]	X				X	X	X	X	X		See Section 8.1

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. 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 first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator prior to IMP administration at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: a treatment cycle is 21 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

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 tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and 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 study.

e For Cycle 4 visits, please refer to PK flowchart in Section 1.5.

f C1D8 and/or C1D15 visits must be performed on site for the following participants only: 1) Participants scheduled to have blood draws for biomarker assessment and/or ADA on Day 8; 2) Participants who will receive IMP on Day 8 and Day 15. For all other participants, these 2 on-site visits may be done remotely as appropriate based on investigator's discretion per institutional standard and local regulations. If this is the case, this must be documented in the source document. Sponsor may decide to cancel safety assessment on C1D8 and C1D15 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 For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.7).

i Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during Treatment Period and as clinically indicated.

j Only for participants who will participate in the intensive PK sample collection.

k AE/SAE assessment: 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).

l If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

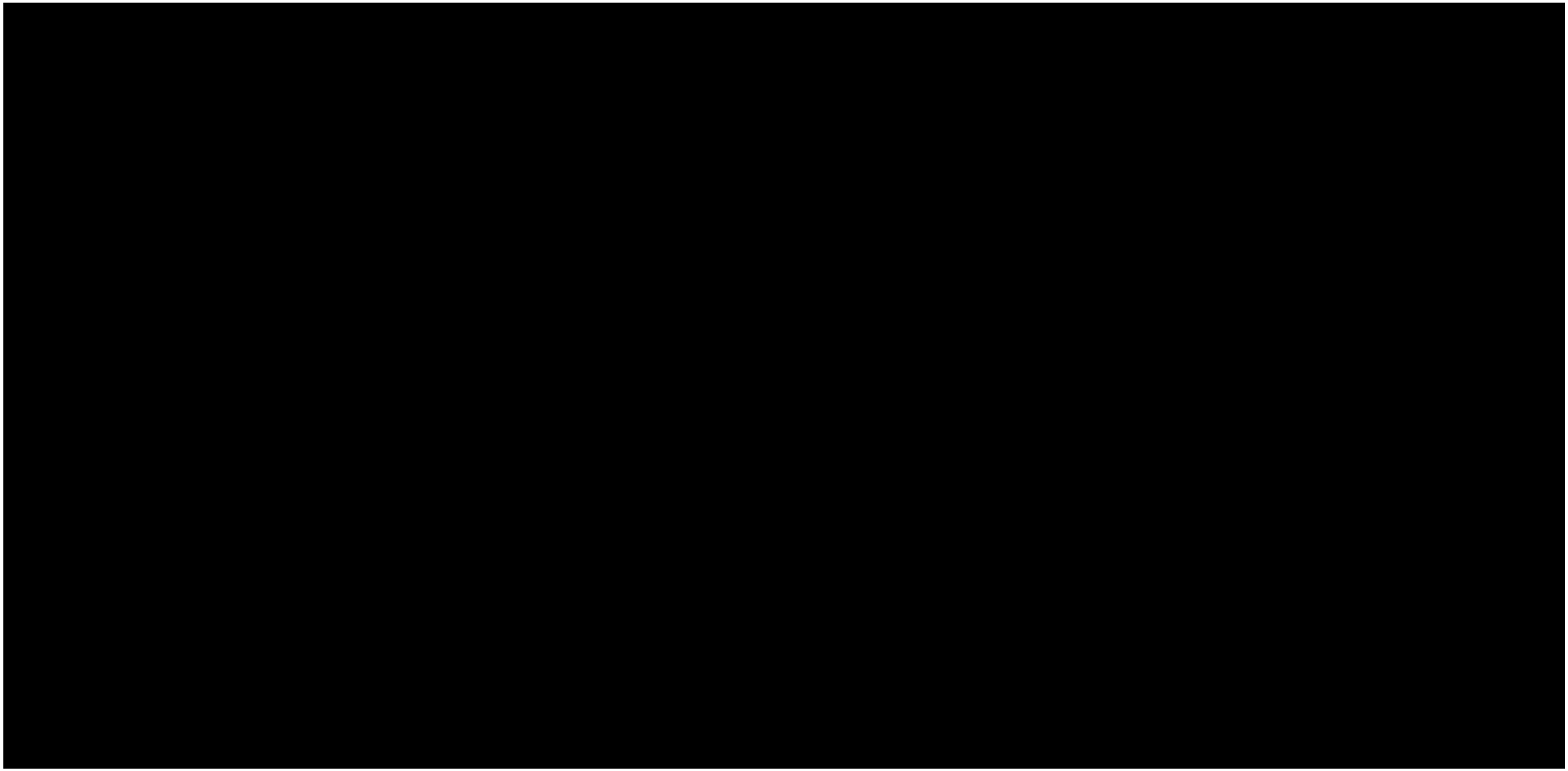
m Will not be done for participants enrolled in China.

n 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 as per protocol tumor assessment (TA) schedule. 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 4 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 have 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.

- CT/MRI: The initial tumor imaging will be performed within 28 days prior to C1D1. 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 of first IMP and 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, during treatment period until PD. Per the primary tumor assessment criteria, after the first documentation of response 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.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; AST=aspartate transaminase; ALT=alanine transaminase; C=Cycle; ANC=Absolute neutrophil count; AP=Alkaline phosphatase; BUN=Blood urea nitrogen; CRF=case report form; CRS=Cytokine release syndrome; CT=computed tomography; [redacted]; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FT4=free thyroxine; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; ICF=Informed consent form; IMP=investigational med[redacted]ed ratio; LDH=Lactate hydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA= multigated acquisition; PD=progressive disease[redacted] PDy=pharmacodynamic; PK=pharmacokinetic; PR=partial response; PS=Performance Status; SpO2= oxygen saturation; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; T3=tri-iodothyronine; TSH=thyroid stimulating hormone; WBC=White blood cells.

1.4 BIOMARKER FLOWCHART



1.5 PHARMACOKINETIC FLOWCHARTS

For participants who will undergo more intensive pharmacokinetic (PK) sampling, the schedule is shown in the flowchart in Section 1.5.1.

For all other participants, the PK sampling schedule is shown in the flowchart in Section 1.5.2.

The sampling time-points for PK and anti-drug antibody (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 Participants with more intensive PK sampling

Cycle	Cycle 1										Cycle 2, 3		Cycle 4									Cycles 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	D1									D8	D1		D1									D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	1	2	4	8	24	48	72	168	SOI	EOI	SOI	EOI	1	2	4	8	24	48	72	SOI	EOI	
SAR444245 PK sample ID	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08		P00[a]	P01[b]	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08	P00[a]	P01[b]	
Sample time window			±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h						±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h			
SAR444245 ADA sample ID[c]	AB00 *a*									AB01	AB00 *a*		AB00 *a*									AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI),

b PK sample must be taken at EOI after flush.

c ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.

In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at EOI + 1 h, +2 h, +4 h, +8 h, +24 h, +48 h and +72 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end of resumed infusion and subsequent samples should be drawn at 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after end of resumed infusion (as per protocol).

ADA: anti-drug antibodies; EOI: End of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: Start of infusion.

1.5.2 All other participants

Cycle	Cycle 1				Cycles 2, 3. 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit
Day	D1			D8	D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	24	168	SOI	EOI	30 (±7) days after last IMP admin
SAR444245 PK sample		P01[b]	P06[c]			P01[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI)
b EOI samples = end of infusion samples. Must be taken at end of infusion precisely
c PK sample can be collected at any time during the second day of the cycle.

ADA: anti-drug antibodies, PK: pharmacokinetic: SOI: start of infusion; EOI: end of infusion

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 complete response (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 ($t_{1/2}$), 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

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models.

The proposed study aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with other anticancer therapies will result in a significant increase in the percentage of participants experiencing an objective response in the setting of various advanced gastrointestinal cancers.

2.2 BACKGROUND

2.2.1 Overall rationale for GI studies

Immune checkpoint inhibitors are approved in most of the indications' proposed cohorts. In esophageal squamous cell carcinoma (ESCC) and gastric or gastroesophageal junction cancer (GC/GEJ), pembrolizumab monotherapy has received approvals as the 2L or 3L+ treatment. However, the benefit is limited to patients whose tumor expresses programmed death-ligand 1 (PD-L1) (CPS ≥1 or ≥10) and the objective response was 16% (CPS ≥1) and 22% (CPS ≥10) (3, 4). Combining SAR444245 (THOR-707) with pembrolizumab is anticipated to expand to population responding to the anti-PD1 and to increase the quality of the response. Such effects have been demonstrated in the PIVOT-02 study for bempegaldesleukin combined with nivolumab in locally advanced or metastatic solid tumors. In this study, 53% ORR including 34% CR was obtained for melanoma (5), 54% ORR for RCC (6), 50% ORR for non-small cell lung cancer (6), 48% ORR for urothelial carcinoma (7) and 13% ORR for triple-negative breast cancer (8), respectively. The ORR was high regardless of PD-L1 status, eg, 50% (PD-L1+) and 45% (PD-L1-) for metastatic urothelial carcinoma (7), 64% (PD-L1+) and 39% (PD-L1-) for melanoma (5), and 57% (PD-L1+) and 54% (PD-L1-) for renal cell carcinoma (6). Based on such evidence, we consider also, that combining THOR-707 with pembrolizumab is anticipated to bring benefit to patients with ESCC and GC/GEJ even in the context of low PD-L1 and could rescue patients who have progressed or relapsed following an anti-PD1/PD-L1 treatment.

In advanced hepatocellular carcinoma, the ICI-based combination regimen (atezolizumab + bevacizumab) has become the new SoC in 1L based on improved durable response and survival. Combining SAR444245 (THOR-707) with ICI will be evaluated to rescue patients who have failed the ICI-based 1L regimen.

Non-MSI-H metastatic colorectal cancer (CRC) is known to not respond to ICI, being qualified as immune excluded or restricted tumors. Combining ICI with SAR444245 (THOR-707) may initiate inflammatory response in the tumor microenvironment and sensitize CRC to anti-PD1.

More details will be provided on the rationale of each cohort and tumor type in appropriate substudies.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SAR444245 may be found in the Investigator's Brochure.

2.3.1 Risk assessment

Safety data from clinical studies conducted with SAR444245 in humans is currently limited to available from the Phase 1/2 first-in-human study (Study TCD16843 [HAMMER], hereafter referred to as HAMMER). Consequently, the assessment of the risks associated with SAR444245 is 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).

Table 5 summarizes potential risks for SAR444245 identified from preclinical experience and from the Phase 1/2 first-in-human (HAMMER) study.

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 (9), 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 (10). 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 embryo lethal effects in rats but there are no adequate well-controlled studies in pregnant women; this information can be extrapolated to SAR444245. Also, since it is not known whether SAR444245 is excreted in human breast milk, nursing mothers cannot participate in this study.

High doses of aldesleukin (IL-2) were associated with decreased expression of enzymes of hepatic metabolism (11). As SAR444245 also exercises IL-2 activity, the Investigator should monitor clinical effects of narrow therapeutic index drugs that are hepatically metabolized.

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 nephrotoxicity and neurotoxicity 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 US label) (12). 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 (CRS) 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 NHP, 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 it 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.

2.3.1.3 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 1 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 (13).

In PIVOT-02, a single-arm, Phase 1/2 study, NKTR-214 plus nivolumab was administered to 38 patients with selected immunotherapy-naïve advanced solid tumors (melanoma, RCC, and non-small cell lung cancer [NSCLC]). Several treatment regimens were explored. The dose of 0.009 mg/kg had excessive toxicity (2 of 3 patients with DLT: Grade 3 hypotension [n=1] & Grade 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 Q3W 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 and 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 became 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 PD-1/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 (14).

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.

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 VLS, while still promoting the 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 other anticancer therapies are justified by the anticipated benefits that may be afforded to participants with gastrointestinal cancer.

2.3.4 Benefit and risk 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

Cancer patients with weakened immune systems are vulnerable to COVID-19 due to the cancer itself and treatments. A large case-control study reported patients with cancer had a higher risk for COVID-19 infection with an odds ratio (OR) of 1.5 compared to those without cancer and those with recent (in the past year) diagnosis of cancer were at a significant increased risk with an OR of 7.1 (15). Among patients with recent diagnosis of cancer, the adjusted OR for COVID-19 infection was 6.5 for liver cancer and 6.4 for colorectal cancer, respectively. COVID-19 increases the severity and complications in patients with cancer. Patients with cancer and COVID-19 had significantly worse outcomes (hospitalization, 47.46%; death, 14.93%) than patients with COVID-19 without cancer (hospitalization, 24.26%; death, 5.26%) and patients with cancer without COVID-19 (hospitalization, 12.39%; death, 4.03%) (15). This was agreed by other studies where the OR for death in COVID-19 patients with cancer was reported from 2.54 to 3.16 compared to those without cancer (16, 17, 18).

The impact of COVID-19 on cancer outcomes differs by cancer type. A meta-analysis of cancer patients with COVID-19 demonstrated gastrointestinal cancer is one of the most common cancer types reported with an estimated rate of 15.2% and its all-cause in-hospital mortality rate (approximately 20%) ranked the third following hematological malignancies and lung cancer (16). In one of these studies, esophageal cancer had a high risk of death (17%), high ICU administration rate (33%) and high risks of severe/critical symptoms (50%), whereas approximately 8%, 23% and 31% were reported respectively for gastrointestinal cancer (19). COVID-19 has caused delays in cancer diagnosis and treatment especially for gastrointestinal cancers, which potentially result in poor clinical outcomes (20, 21, 22). Furthermore, patients with advanced and metastatic gastrointestinal cancer often suffer from gastrointestinal symptoms and chronic bleeding, thus experiencing malnutrition, poor immune status and anemia (22). In addition, patients may suffer from poor mental status such as anxiety or depression during the pandemic. All of these can lead to further deterioration of patients' condition and expose them to high risk of getting COVID-19 and developing more severe clinical outcomes. To that end, trial participation will proceed during the COVID-19 pandemic, however, measures will be taken to mitigate the potential risks of SARS-CoV-2 infection to trial participants.

Testing for SARS-CoV-2 infection during the screening phase should be at Investigator's discretion and should also follow local/international guidelines (eg, patients who are asymptomatic but with high risk of infection, 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 infection, dose modification of study intervention should be based on the recommendations provided in Section 6.5. 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) (23)
- European Society for Medical Oncology (ESMO) (24)

2.3.4.1.2 Risks related to study treatment

SAR444245 has the potential to induce CRS which could exacerbate the manifestations of COVID-19 infection. It is, however, worth noting that 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 10.9, 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.
- 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 gastrointestinal cancer during the COVID-19 pandemic. The 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 other anticancer therapies	• 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)
Secondary	
• To assess the safety of SAR444245 in combination with other anticancer therapies	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (2)
• To assess other indicators of antitumor activity	• Time to response (TTR), defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1 • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first • Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months determined by Investigator per RECIST 1.1. • Progression-free survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by Investigator as per RECIST 1.1 or death due to any cause, whichever occurs first
• To assess the pharmacokinetics of SAR444245 in combination with other anticancer therapies	• Plasma concentrations and where applicable PK parameters of SAR444245
• To assess the immunogenicity of SAR444245	• Incidence of anti-drug antibodies (ADAs) against SAR444245
Exploratory	

For China, please see Section 10.7 for details.

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 gastrointestinal 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 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with other anticancer therapies in participants with advanced or metastatic gastrointestinal cancer.

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals. This design is with the flexibility to open new treatment cohorts as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity.

The information that is introductory and common to all cohorts is included in the present document ("Master Protocol"), and cohort-specific elements are included in separate substudies. This study is designed with the flexibility to open new treatment arms or add new indications as permitted by scientific rationale.

A graphical presentation of the study schema is shown in the individual substudy.

Interactive Response Technology (IRT) will be used to control recruitment, assignment per site and to facilitate the handling, management, and accountability of 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 progressive disease (PD), unacceptable adverse event (AE) or other full permanent discontinuation criteria as described in Section 7; or completion of Cycle 35 (if applicable).
- **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, whichever comes first. 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 PD** or who **complete 35 cycles of treatment without PD** will be followed every 3 months ±7 days from last IMP administration, for safety (as per Schedule of Activities [SoA]) and tumor imaging assessments 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 PD** will be followed for safety 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. Updated survival status may be requested by the Sponsor at any time during the study. Survival Phone Call Follow-up will continue until death, participant request to discontinue from follow-up, or cut-off date for the given cohort final analysis has been reached, or upon cancellation of Survival follow-up in the given cohort at the discretion of the Sponsor at any prior timepoint whichever occurs first.

The cohort cut-off for the primary ORR endpoint analysis for each individual cohort is estimated to be approximately 9 months from the date of the last participant first infusion. This would allow the possibility to observe the response of the last participant for 6 months, assuming there is a response at first treatment assessment.

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 18 months from the corresponding cohort LPI. After this cut-off date for the final analysis, the participants of the given cohort still receiving study treatment in that specific cohort will be followed up as the cohorts after early termination described in Section 10.1.9.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with other anticancer therapies will result in a significant increase in the percentage of participants experiencing an objective response.

The design of the 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 as a benchmark to show outstanding ORR. The ORR will be assessed using RECIST 1.1 for participants with advanced and metastatic gastrointestinal cancer. The objective response will be assessed per Investigator as primary endpoint. Central imaging reading may be done retrospectively if significant activity is observed.

4.2.1 Participant input into design

There was no participant involvement in the 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/m² QW is available as of 18 June 2021. SAR444245 24 µg/kg Q3W pembrolizumab combination and cetuximab combination dose level have been cleared by HAMMER Safety Review Committee based on this data cut-off.

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), 32 µg/kg (n=6) and 40 µg/kg (n=2).

In combination with pembrolizumab, SAR444245 has been administered Q3W at the doses of 8µg/kg (n=4), 16µg/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 reaction (occurred in 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%).

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, 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 post-dose 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 below, Sponsor proposes to evaluate the clinical benefit of SAR444245 24 µg/kg in this Phase 2 study.

1. SAR444245 monotherapy up to 32 µg/kg Q3W, pembrolizumab combination up to 32 µg/kg Q3W and cetuximab combination 24 µg/kg Q3W are all cleared in HAMMER study.
2. Sustained relevant PDy effect in blood, higher at higher dose, was documented in participants;
3. And overlapping toxicities not suggested by comparing safety data from SAR444245 monotherapy cohort, SAR444245 in combination with pembrolizumab cohort, or SAR444245 in combination with cetuximab cohort. Though theoretically, combining SAR444245 with either pembrolizumab or cetuximab may lead to increase and/or severity of certain AEs (detailed in Section 2.3.1 of the substudies).

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

The inclusion criteria listed in the master protocol are only those applicable to all the participants common to all substudies. For additional substudy specific criteria, refer to the particular substudy.

Participants are eligible to be included in the study only if all of 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

I 02. Measurable disease:

At least 1 measurable lesion per RECIST 1.1 criteria. Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site.

Weight (not applicable)

Sex, contraceptive/barrier method and pregnancy testing requirements

I 03. 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 3 days [corresponding to time needed to eliminate SAR444245] after the last dose of SAR444245:

- 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 Section 10.4 Appendix 4 when having sexual intercourse with a woman of childbearing potential (WOCBP) 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 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 Section 10.4 Appendix 4 during the intervention period (to be effective before starting the intervention) and for at least 120 days (for Cohort A, B1, B2, B3, C, and D1) or 60 days (for Cohort D2) [corresponding to the time needed to eliminate any study intervention(s)-] 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 72 hours before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 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 04. Capable of giving signed informed consent as described in Section 10.1 Appendix 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. For additional individual substudy specific criteria, refer to the particular substudy:

Medical conditions

E 01. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2.

E 02. Predicted life expectancy ≤3 months.

E 03. 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 at least 2 weeks prior to first IMP administration.
- 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 as per protocol tumor assessment (TA) schedule.

E 04. History of allogenic tissue/solid organ transplant.

E 05. 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 06. 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 within 28 days prior to first IMP administration.

E 07. 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 08. 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 15), or other infection that is not controlled.

E 09. 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 v5.0), or myocardial infarction.

E 10. Ongoing AEs (caused by any prior anti-cancer therapy ≥Grade 2 (NCI-CTCAE Version 5.0). Participants with Grade 2 peripheral neuropathy, or Grade 2 alopecia, are permitted. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

E 11. 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 12. History of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.

E 13. Participant who has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

E 14. Receipt of a live or live attenuated-virus vaccine within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 15. HIV-infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease or known uncontrolled infection with 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.

See instructions specific to Germany and Italy at screening in Appendix 2 (Section 10.2) and Appendix 7 (see Section 10.7).

E 16. 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.

See instructions specific to Germany and Italy at screening in Appendix 2 (Section 10.2) and Appendix 7 (see Section 10.7).

E 17. Known second malignancy either progressing or requiring active treatment within the last 3 years. Participants with non-melanomatous skin cancer or cervical cancer that has been curatively surgically resected are eligible.

E 18. Known severe hypersensitivity (≥ Grade 3) 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 19. Participants with baseline SpO2 ≤92% (without oxygen therapy).

Prior/concomitant therapy

E 20. Has received prior IL2-based anticancer treatment.

E 21. Is unable or unwilling to take premedication.

E 22. Participants treated under anti-hypertensive treatment who cannot temporarily (at least 36 hours) withhold antihypertensive medications prior to each IMP dosing.

Prior/concurrent clinical study experience

E 23. Current enrollment or past participation in a study of an investigational treatment or an investigational device within 28 days prior to the first dose of study treatment.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational treatment.

Organ and bone marrow function

E 24. Absolute neutrophil count <1500 /uL (1.5×10^9/L) (after at least one week off G-CSF).

E 25. Platelets <75 × 10^3 u/L for participants in Cohort C and platelets <100 × 10^3 u/L for participants in all other cohorts (after at least 3 days without platelet transfusion).

E 26. 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 27. 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 28. Aspartate aminotransferase and/or alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases or participants in Cohort C).

E 29. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² (Modification of Diet in Renal Disease [MDRD] Formula).

E 30. 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.

Other exclusions

E 31. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 32. Any country-related specific regulation that would prevent the participant from entering the study - see Section 10.7 Appendix 7 (country-specific requirements).

E 33. 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 34. 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 35. Any specific situation during study implementation/course that may raise ethics considerations.

E 36. 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 be provided with 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. 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. Rescreened participants should be assigned a different participant number as for the initial screening.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/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 10.9.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

Participants will receive study treatment until PD, unacceptable toxicity, other permanent discontinuation criteria as described in Section 7, or completion of Cycle 35 (if applicable).

6.1.1 Investigational medicinal product (IMP)

Details of each SAR444245 are shown in Table 2.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.9.

Preparation and administration of SAR444245 are detailed in the pharmacy manual. Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3.

Table 2 - Overview of IMP administered

Intervention name	SAR444245
Type	Biological
Dose formulation	Concentrate for solution for infusion
Unit dose strength(s)	2.0 mg/mL
Dosage level(s)[a]	24 µg/kg Q3W
Route of administration	IV infusion
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	Supplied in a single-dose vial in a treatment box. Each vial contains 2 mg/mL with an extractable volume of 1 mL. Each vial and treatment box will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	NA

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 e-CRF. Study sites should make every effort to target infusion timing 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.

6.1.2 Non-investigational medicinal products

Non-investigational medicinal products include the premedication administered for SAR444245.

6.1.2.1 Premedication for SAR444245

All participants will receive the following premedication to prevent or reduce the acute effect of 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 PO) (or equivalent), and then optionally thereafter as needed.
- Diphenhydramine 25 to 50 mg IV or PO (or equivalent, eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter as needed.

SAR444245 premedication may be optional after 4 cycles:

- For a participant who has no IRR for the first 4 cycles, premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the participant experiences an IRR (any grade), 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 Cycle 5. If no IRR is observed during Cycle 5 without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during Cycle 5 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 or alternative therapies per site practice in CRS management should be available at the site at all times in the event that a participant requires rapid intervention for the treatment of severe CRS. Please refer to Section 6.5 of individual substudies 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 8.3.9).

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 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 DOSE MODIFICATION

Please see respective substudy protocols.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

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

6.7 TREATMENT OF OVERDOSE

There is no specific antidote for overdose with SAR444245.

If overdose occurs (see Section 8.3.8 for definitions), 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 irAEs are provided in the individual substudies.

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.

6.8 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 study intervention may be required. The Investigator is to discuss prohibited medication/vaccination 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.

6.8.1 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 28 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 (25).

6.8.2 Prohibited concomitant medications

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Investigational agents other than specified in this protocol.
- Radiotherapy for tumor control (please refer to Section 6.8.1 for allowed radiotherapy).
- Live or live attenuated virus vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live-virus 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 AEs when indicated (irAE, CRS, ICANS, IRR, see Section 6.5 of individual substudies),
  - 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.

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.
  - Poor compliance to the study protocol.
  - Completion of 35 cycles when applicable.
  - 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 the dose modification and toxicity management guidelines (see individual substudy protocols), 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 6.5 of individual substudies (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.

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 (Section 10.9). 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 has 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 9 Contingency Measures for a regional or national emergency (Section 10.9) 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, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, 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 withdrawn from the study 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 (see Section 10.1.9).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures are summarized in this section and their timing is presented in the SoA (Section 1.3). 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 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, echocardiography 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 10.9.

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. 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 may be done at the discretion of the Investigator when clinically indicated.

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. Study sites must retain tumor assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

Assessment of tumor response will be conducted using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (see Section 10.8) 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 is measured radiologically according to RECIST 1.1 criteria (see 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 (preferred) or MRI is an Investigator decision. Once the choice of CT scan or MRI has been made, the same imaging technique should be used in a participant throughout the trial.

Baseline imaging should include all known target lesions. Baseline scans must evaluate extent of disease, including imaging of chest, abdomen, and pelvis and any other locations with suspicion or evidence of disease involvement. This may be accomplished with CT chest, abdomen, and pelvis with contrast, or CT chest with contrast and MRI abdomen/pelvis with gadolinium.

The initial CT/MRI tumor imaging will be performed within 28 days prior to C1D1. 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 of first IMP and if clinically indicated. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). Per the primary tumor assessment criteria, after the first documentation of response 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 anticancer therapy.

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. If lesions are identified, the lesions must be treated, regardless of symptoms. 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 prior anticancer 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 4 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.

RECIST 1.1

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention).

8.2 SAFETY ASSESSMENTS

The main anticipated adverse effect for the combination of SAR444245 with other anticancer therapies 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. When clinically indicated, on-treatment ECG, LVEF, and troponin 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

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- 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 including temperature, pulse rate, respiratory rate, and blood pressure will be assessed after 5 minutes rest
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively; 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 in an in-patient setting.
- At Investigator's discretion, participants may have intensive vital sign monitoring: to 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 in-patient setting.
- From Cycle 2 to Cycle 4 study therapy will be administered for all participants in out-patient clinic with vital signs taken at baseline, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.
- From Cycle 5, vital signs will be measured at Pre-dose.

8.2.3 Electrocardiograms and LVEF

- Includes single 12-lead ECG, LVEF, and troponin that will be performed at screening and troponin at Cycle 4 Day 1, then, as clinically indicated.
- At Cycle 1 Day 1, ECG will be obtained, at pre-dose and at end of SAR444245 infusion.
- 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: Troponin will be performed at Cycle 4 Day 1. 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 relevant changes occurring during the study as an AE. 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 tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests 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 I 03 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 72 hours prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 120 days (for Cohort A, B1, B2, B3, C, and D1) or 60 days (for Cohort D2) 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.

AE 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 cessation of study treatment.

All SAEs and AESIs will be collected throughout the 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). 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 10.3), 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 an 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).
- 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 an 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 120 days (for Cohort A, B1, B2, B3, C, and D1) or 60 days (for Cohort D2) 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 AESI 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 Appendix 3 [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 Appendix 4 [Section 10.4])
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose of IMP is defined as: 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 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*.

  For Participants with HCC, please refer to substudy 03 Corhort C.

*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

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 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.

For China, please see Section 10.7 for details.

8.5 GENETICS AND/OR PHARMACOGENOMICS

[redacted]

8.6 BIOMARKERS

[redacted]

[redacted]

8.7 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.

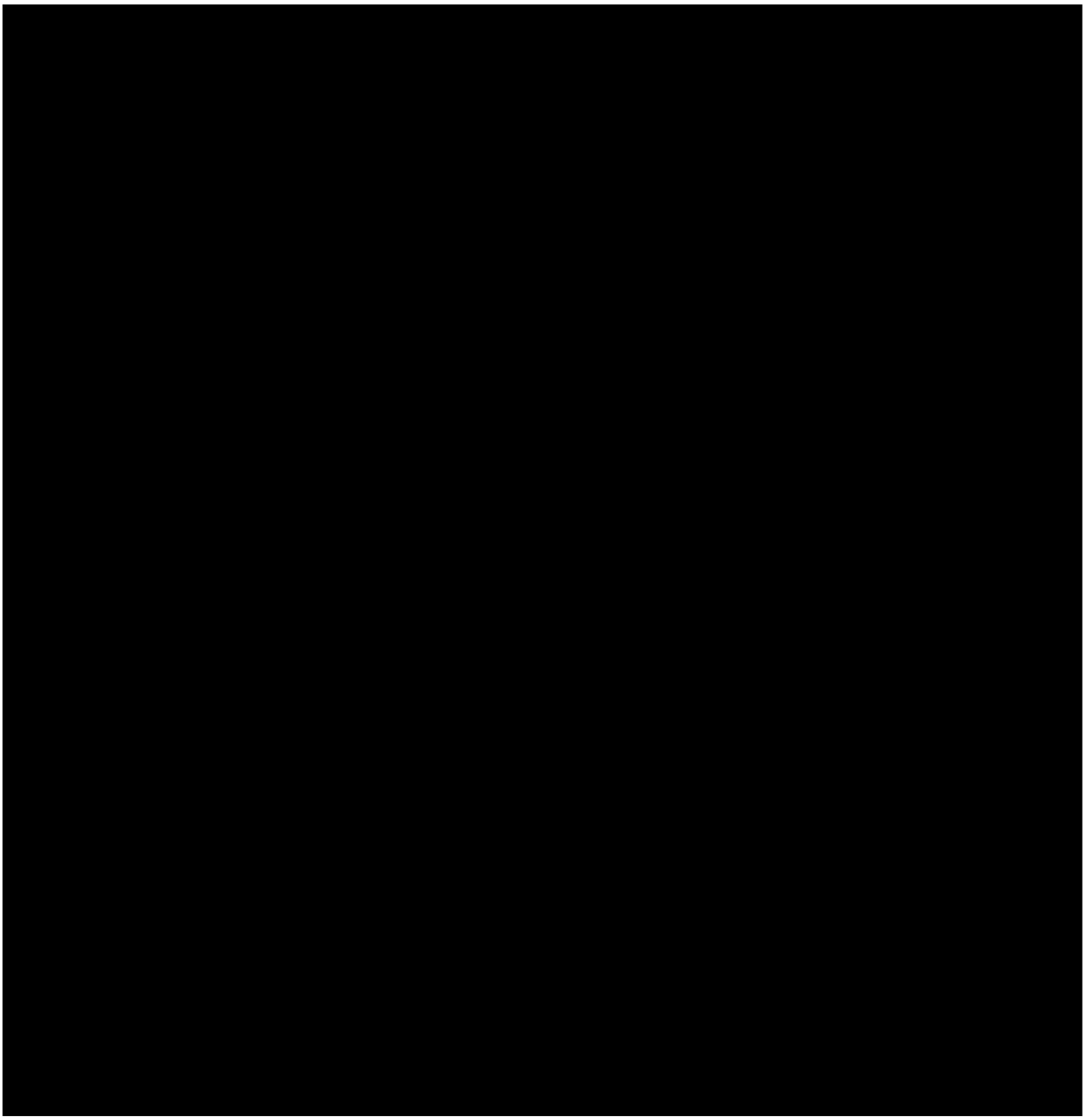
Anti-drug antibody (ADA) samples remaining after determination of immunogenicity may be kept for possible exploratory analysis of biomarkers. The exploratory data will not be included in the study report but will be kept on file.

For China, please see Section 10.7 for details.

8.8 HEALTH ECONOMICS

No health economics data will be collected.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH



9 STATISTICAL CONSIDERATIONS

Please refer to substudies protocols for additional statistical considerations.

9.1 STATISTICAL HYPOTHESES

This study is designed to assess antitumor activity, safety, pharmacokinetic (PK), pharmacodynamic (PDy) and immunogenicity data on SAR444245 when combined with other anticancer therapies in participants with gastro-intestinal cancer. As the study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

9.2 SAMPLE SIZE DETERMINATION

Number of participants to be enrolled in each cohort is described in the individual substudy.

9.3 POPULATIONS FOR ANALYSES

The following populations for analyses are defined (Table 3):

Table 3 - 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 other anticancer therapies).
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.
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 (SAP) 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, 90% CIs will be provided for primary and secondary efficacy endpoints for descriptive purposes only.

All efficacy analyses will be performed on the efficacy population and analyzed by cohort and pooled cohorts (if applicable). Objective response rate, as well as all other efficacy variables will be derived using the local radiologist's/Investigator's assessment for all cohorts. Unless otherwise specified, the assessments are based on RECIST 1.1.

All safety analyses will be performed on the exposed population by cohort and overall (if applicable). A 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

For all cohorts, the ORR is defined as the proportion of participants who have a confirmed CR or PR as per Investigator's assessment.

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.

ORR and BOR will be summarized with descriptive statistics. In addition, two-sided 90% CIs will be computed using the Clopper-Pearson method. All objective responses need to be confirmed by a subsequent assessment performed at least 4 weeks apart from the initial response observation.

9.4.3 Secondary endpoint(s)

The secondary endpoints include safety, efficacy (TTR, DoR, CBR, PFS per RECIST 1.1), immunogenicity, and PK.

9.4.3.1 Time to response

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

Time to response will be defined as the time from the date of first IMP administration to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed.

9.4.3.2 Duration of response

The DoR will only be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.

The duration of response will be defined as the time from the date of 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 progressive disease 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 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 with descriptive statistics using Kaplan-Meier methods. The median DoR and associated 90% CI will be provided.

9.4.3.3 Clinical benefit rate

The CBR will be defined as the proportion of participants with clinical benefit (confirmed CR or PR as BOR, or SD lasting at least 6 months). Specifically, participants will be considered as clinical benefit responders if they achieve a CR or PR as BOR, or have 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.

9.4.3.4 Progression-free survival (RECIST 1.1)

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 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 anticancer 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 anticancer 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.

9.4.3.5 Adverse events

All AEs will be categorized according to NCI-CTCAE v5.0 (except for CRS and ICANS that will be graded using ASTCT criteria) and classified by system organ class (SOC) and Preferred Term (PT) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

- 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 treatment-emergent 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
- Grade ≥3 TEAEs
- Grade 5 TEAEs (any TEAE with a fatal outcome during the treatment-emergent period)
- Serious TEAEs
- Serious treatment-related TEAEs
- TEAEs leading to permanent partial intervention discontinuation (any of the IMP components)
- TEAEs leading to permanent full intervention discontinuation
- Treatment-related TEAEs
- Treatment- related TEAEs Grade ≥3

Number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE v 5.0 or ASTCT grade (all grades and Grade ≥3). Missing grades, if any, will be included in the "all grades" category. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to permanent discontinuation of SAR444245, or permanent discontinuation of other anticancer therapies in combination, 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-emergent period, post-treatment period) 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.

9.4.3.6 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.

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.

9.4.3.7 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).

Plasma concentrations (or where applicable PK parameters) of SAR444245 will be summarized with descriptive statistics by each cohort.

9.4.4 Tertiary/exploratory endpoint(s)

9.4.4.1 Exploratory antitumor indicators

[redacted]

[redacted]

9.4.5 Other safety analysis

All vital signs will be summarized according to potentially clinically significant abnormalities (PCSA).

9.4.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9.

9.5 INTERIM ANALYSES

No formal interim analyses are planned. However, for each cohort, in order to support project strategic planning and design of future studies, informal interim analyses will be conducted during the study without enrollment hold (eg, after half of the planned number of participants have undergone two post-baseline tumor assessment or have discontinued study treatment, whichever is earlier).

In addition, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the Data Monitoring Committee (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. Occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants will trigger ad hoc DMC. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

The cohort cut-off for the primary ORR endpoint analysis is estimated to be approximately 9 months from the date of the last participant first infusion. This would allow the possibility to observe the response of the last participant for 6 months, assuming there is a response at first treatment assessment.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 18 months from cohort LPI. After this cut-off date for the final analysis, the participants still receiving study treatment in that specific cohort will be followed up as the cohorts after early termination described in Section 10.1.9.

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, Investigator Brochure, 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 (as per Sanofi policy) 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 (if allowed by local regulations) 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 (if allowed by local regulations), 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 9: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.9).

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 these data 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 pharmaceutical 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 Committees structure

Data Monitoring Committee

Independent from the Sponsor and Investigators, the DMC role will be to 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 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 of 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). Should the Sponsor decide to pause recruitment in a cohort to allow decision making, the Investigator should pause all screening activities until further notice.

If the study or a given cohort is early terminated the patients who are receiving and benefitting from study treatment as per Investigator judgment may continue study treatment provided by the Sponsor 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. This recommendation also apply for patients still on study treatment at the final cut-off date for a given cohort.

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

Table 4 - Protocol-required laboratory assessments

Laboratory tests	Parameters
Hematology[a]	Platelet count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Urea or urea nitrogen
	Creatinine and eGFR (MDRD formula[b])
	Glucose
	Potassium
	Sodium
	Corrected Calcium
	Phosphate
	Chloride
	Magnesium
	Bicarbonate[c]
	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
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT])
Routine urinalysis[d]	Specific gravity, pH, glucose, protein, blood, ketones, and leukocytes by dipstick
	Microscopic examination (if blood or protein is abnormal)

Laboratory tests	Parameters
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)[e] Serology (hepatitis B surface antigen [HBsAg], hepatitis C virus antibody), Hepatitis B viral load, HCV RNA level, CD4 counts & HIV viral Load[f] Troponin The results of each test must be entered into the e-CRF

NOTES :

a Blood Chemistry/hematology should be done with an overnight fasting if possible (should not interfere with hydration requirements). It will be performed weekly on D1 pre-dose, D8 and D15 during Cycle 1, then on Day 1 of every cycle up to Cycle 12, then every other cycle during Treatment Phase. 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.

b Modification of Diet in Renal Disease (MDRD) equation: Glomerular filtration rate (mL/min/1.73 m^2) = 175 × (Serum Creatinine [mg/dl])-1.154 × (Age)-0.203 × (0.742 if Female) × (1.212 if African American)

c 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)

d Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during the Treatment period and as clinically indicated.

e Pregnancy Test: Women of childbearing potential must have a negative urine pregnancy test result within 72 hours prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 120 days (for Cohort A, B1, B2, B3, C, and D1) or 60 days (for Cohort D2) 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.

f Participants with known HIV infection under antiretroviral treatment should have HIV viral load & CD4+ count done at screening 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, hepatitis B and C serology at screening will be tested in any countries where mandatory as per local requirements (see Section 10.7).

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: 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 V5.0 definitions (except for ICANS and CRS that will be graded using ASTCT criteria integrated with central laboratory cytokine results):

- 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 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 that 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 Investigator’s Brochure (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 an 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, if available 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 submitted documents.
- 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 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.
- 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 via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool 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 data collection tool 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 and sperm for up to the number of days specified respectively for each cohort in the 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.

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

China

- Global exploratory endpoints and relevant collection procedures, as described in Section 3 and Section 1.3, are optional for Chinese participants.
- Exploratory genetic and biomarker sample will not be collected for participants in China. Therefore, exploratory genetic and biomarker sample collection as described in Section 1.3, Section 8.5 and Section 8.6 are not applicable to participants in China.
- In accordance with local requirements, use of biological samples as described in Section 8.9 is not applicable for participants in China. All residual mandatory samples collected from participants in China have to be destroyed upon clinical study report (CSR) completion at the latest.
- Protein expression sample as described in Section 10.2 will not be collected for participants in China.

Germany

Section 5.2 Exclusion Criteria (see Section 5.2)

E 15. HIV-infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease or known uncontrolled infection with 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/mm3 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.

HIV serology at screening will be tested for German participants.

E 16. 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.

Serology for hepatitis B and C at screening will be tested for German participants.

Italy

Serology for HIV, hepatitis B and C at screening will be tested for Italian participants.

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

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

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. 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.

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 be 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 close 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 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; 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: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL 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).

10.9.1 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).

10.9.2 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 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.

10.9.3 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.

10.9.4 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.

10.10 APPENDIX 10: RISK ASSESSMENT

The information shown in Table 5 reflects the clinical safety data available at the time of Edition 4 of the SAR444245 IB. Please always refer to the latest version of the IB for the most up-to-date safety data.

Table 5 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the THOR-707-101/HAMMER study has reported such AE as detailed in the SAR444245 IB.	SAR444245 Standard pre-medication Dose modification and treatment guidelines for SAR444245 infusion related reactions are provided in individual substudies.
Hypersensitivity, including anaphylaxis	SAR444245 Not observed in non-clinical toxicology studies. No reports of anaphylaxis in the HAMMER study to date.	Exclusion of participants with known hypersensitivity to or contraindication for any components of SAR444245, PEG, or pegylated drugs.
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.	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.	Study to be conducted at sites experienced with CRS management, with bed available in ICU.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	A minority of patients in the HAMMER study have reported such AE as detailed in the SAR444245 IB.	Premedication with paracetamol, diphenhydramine (or equivalent medications) Hydration guidelines, including management of anti-hypertensive treatment around the time of infusion, are provided. Extensive post-dosing monitoring will be performed. Dose modification and treatment guidelines are provided in individual substudies.
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 are provided in individual substudies.
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 are presented in the SAR444245 IB. Transient lymphopenia has also been observed.	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 individual substudies).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
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 SAR444245 IB.	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 individual substudies.
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.	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 individual substudies.
Neurological AEs, including 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 ug/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	Exclusion of participants with active brain metastases or leptomeningeal metastases. See E 03 for details. Guidelines for the management of ICANS are provided in individual substudies.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	tocilizumab and steroid. This patient later discontinued.	
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 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 SAR444245 IB.	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 09 for details. 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.	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 individual substudies.

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.	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 03. 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.	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%)(26, 27, 28).	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.	Strict adherence to the protocol; Adequate and verified training of staff at investigational sites. See Section 6.8.
Study procedures		
Biopsies of tumor tissue are expected during the trial.		Strict adherence to the guidance in the protocol

10.11 APPENDIX 11: ASTCT ASSESSMENT FOR ICANS AND CRS

Table 6 - 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 7 - 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 (participant is unrousable and unable to perform ICE).
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Participant 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 V5.0, 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 V5.0.

Abbreviations: ASTCT=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 8 - 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 v5.0 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: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=Bi-level positive airway pressure CPAP= Continuous Positive Airway Pressure; CRS=Cytokine release syndrome.

Source: (2).

10.12 APPENDIX 12: ABBREVIATIONS

ADL: activities of daily living
AESI: adverse event of special interest
BOR: best overall response
CBR: clinical benefit rate
CR: complete response
[redacted]
ICANS: immune cell-associated neurotoxicity syndrome
IHC: immunohistochemistry
IR: infusion reaction
irAE: immune-related adverse event
IRR: infusion-related reaction
MedDRA: medical dictionary for regulatory activities
MTD: maximum tolerated dose
ORR: objective response rate
[redacted]
PD: progressive disease
[redacted]
PFS: progression-free survival

PK:	pharmacokinetic
PR:	partial response
PT:	preferred term
RCC:	renal cell carcinoma
SAE:	serious adverse event
TEAE:	treatment emergent adverse event
TLS:	tumor lysis syndrome
[redacted]	
TRAE:	treatment-related adverse event
TTR:	time to response
VLS:	vascular leak syndrome
WOCBP:	woman of childbearing potential

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

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

10.13.1 Amended protocol 01 (30 August 2021)

This amended protocol (Amendment 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 overall rationale for the amendment is to include stopping rules for futility for each cohort, update the rules for dose modification in case of treatment-related adverse events (TRAEs), and clarify the population for Cohorts B1, B2 and B3 in substudy 02.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 4.1 Overall design	The follow sentence has been deleted “or until start of another anticancer therapy or final cohort cut-off, whichever comes first” for the reason leading to EOT for the participants who discontinue study treatment with PD,	For consistency and clarification.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SOA)	Footnote i "Only for participants who will participate in the intensive PK sample collection" has been added for Hospitalization.	Correction for consistency and clarity.
Section 1.5 Pharmacokinetic flowcharts	The frequency of sampling for PK and ADA has been increased to obtain data every cycle for the first 3 cycles, every other cycle for 4 samples, then every 4th cycle.	Regulatory Authorities (FDA) request to generate more comprehensive evidence.
Section 4.3 Justification for dose	The following text "Overlapping toxicities not expected for SAR444245 in combination with pembrolizumab or cetuximab, as suggested by safety data observed" has been changed to "And overlapping toxicities not suggested by comparing safety data from SAR444245 monotherapy cohort, SAR444245 in combination with pembrolizumab cohort, or SAR444245 in combination with cetuximab cohort. Though theoretically, combining SAR444245 with either pembrolizumab or cetuximab may lead to increase and/or severity of certainly AEs (detailed in Section 2.3.1 of the substudies)."	For consistency
6.8.2 Prohibited concomitant medications	The following sentence has been removed: "Participants requiring medication(s) that are metabolized by the liver and have narrow therapeutic index require close monitoring (drug blood levels or other surrogate of drug exposure) when on study treatment. If a participant cannot be closely monitored, he/she should be removed from the trial."	Based on new de-risking in-vitro data
Section 8.2.2 Vital signs	"in an in-patient setting" has been added for vital sign measured at Cycle 1 Day 1. The following sentence has been added:" From Cycle 5, vital signs will be measured at Pre-dose".	For clarity.
Section 8.2.3 Electrocardiograms and LVEF	The following sentence has been added: "At Cycle 1 Day 1, at pre-dose and at end of SAR444245 infusion, ECG will be obtained".	Regulatory Authorities (FDA) request to generate more comprehensive evidence.

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim analyses	The following sentence “However, for each cohort, in order to support project strategic planning and design of future studies, informal interim analyses may be conducted during the study (eg…) ” has been changed to “However, for each cohort, in order to support project strategic planning and design of future studies, informal interim analyses will be conducted during the study without enrollment hold (eg..,)”.	For clarity.
Throughout	Minor editorial updates	For consistency and clarification.

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Approve & eSign	[redacted] Clinical [redacted]

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AMENDED CLINICAL TRIAL PROTOCOL 02 (SUBSTUDY 01)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants with advanced and metastatic esophageal squamous cell carcinoma**
Protocol number:	**ACT16902-S01**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab for the treatment of participants with esophageal squamous cell carcinoma**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette,** **91380 Chilly-Mazarin,** **France**
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02 (Substudy 01)	All	12 January 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 01)	All	30 August 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 01)		20 July 2021, version 1 (electronic 1.0)

Amended protocol 02 (12 January 2022)

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 main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Belgian, Italian, German (Federal Institute for Drugs and Medical Devices [BfArM]), and South Korean Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA is provided for this substudy with procedures taken from the master protocol. And the previous footnote a for endocrine function tests has been renumbered as footnote j in the current document	Regulatory Authorities (BfArM) request.
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessment of any potential cardiotoxity.

Section # and Name	Description of Change	Brief Rationale
1.4 Biomarker flowchart	A complete Table of biomarker flowchart is provided for this substudy with biomarker sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.
1.5 Pharmacokinetic flowcharts	A complete Table of pharmacokinetic (PK) flowcharts are provided for this substudy with PK sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Cohort-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants with advanced and metastatic esophageal squamous cell carcinoma

Brief title: A study of SAR444245 combined with pembrolizumab for the treatment of participants with esophageal squamous cell carcinoma

Rationale:

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 programmed cell death-1 (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 CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of complete responses (CR) and tumor-free surviving animals compared to each agent 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 non-alpha-IL2 SAR444245 with the anti-PD1 antibody pembrolizumab will result in a significant increase in the percentage of patients experiencing an objective response in the setting of advanced unresectable or metastatic esophageal squamous cell carcinoma (ESCC).

Objectives and endpoints

Please refer to the master protocol.

Overall design:

Please refer to the master protocol.

Brief summary:

Cohort A will assess SAR444245 adding on to pembrolizumab in participants with advanced unresectable or metastatic ESCC, regardless of PD-L1 expression (any combined positive score [CPS]), who have received at least one but no more than two prior lines of treatment and have progressed after primary or secondary resistance to an anti-PD-1/PD-L1 based regimen (detailed in Section 5.1). Patients with known high microsatellite instability (MSI-H) will not be eligible, but the determination of the MSI status will not be required for enrollment.

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

Figure 1 - Overall study schema - Substudy 01

Abbreviations: 2-3L: second-line or third-line; CPS: combined positive score; ESCC: esophageal squamous cell carcinoma; N: number; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in Cohort A.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration for a participant in Cohort A. For treatment period, the completion of Cycle 35 is applicable for Cohort A.

Study intervention(s)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab

- **Formulation**: Keytruda® (pembrolizumab) as 100 mg/4 mL (25 mg/mL) solution in single-dose vials
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle for **up to 35 cycles**.

Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

SAR444245

SAR444245 formulation, route of administration, and dose regimen as described in the master protocol. Treatment duration for Cohort A is up to 35 cycles.

Noninvestigational medicinal products

Please refer to the master protocol.

After 4 cycles, in case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, premedication no longer needs to be administered.

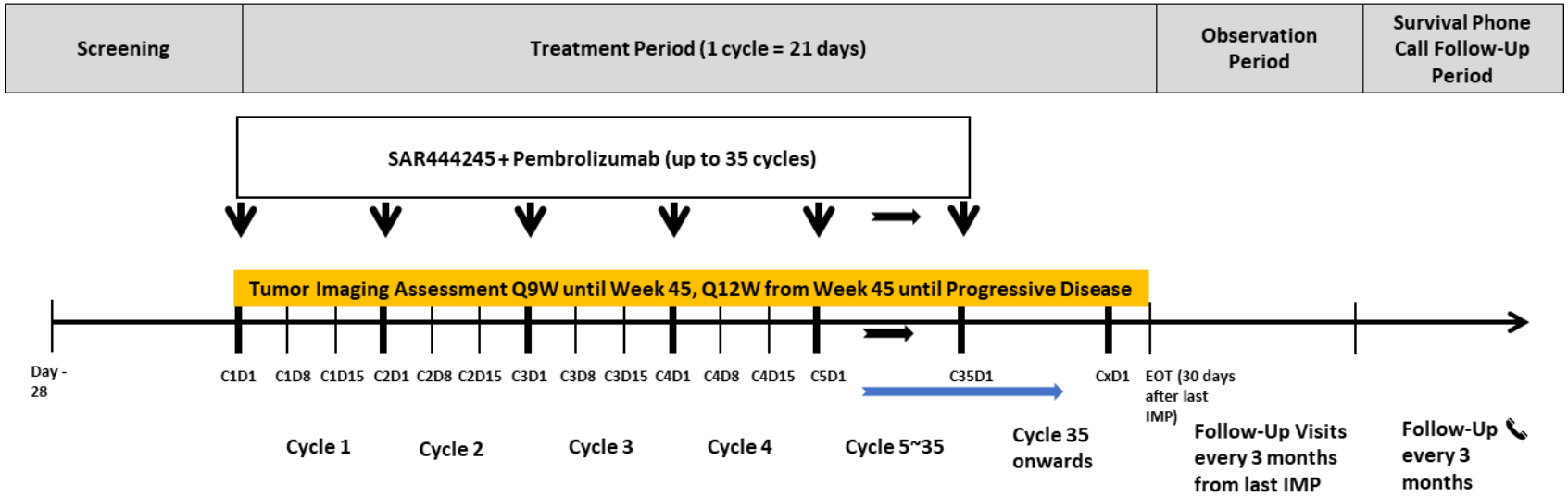
Statistical considerations:

Please refer to the master protocol.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 2 - Graphical study design - Cohort A



C=Study cycle; D=Study day; EOT=end of treatment; IMP=Investigational medicinal product; Q9W=every 9 weeks; Q12W=every 12 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Informed consent	X										
Inclusion and exclusion criteria	X										
IRT contact	X	X			X	X					
Demography, medical/surgical and disease history	X										See Section 8 of the master protocol
Body Weight / Height[g]	X	X	X	X	X	X	X				
Full physical examination	X					X					See Section 8.2.1 of the master protocol
Directed Physical examination		X	X	X	X		X				See Section 8.2.1 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Vital Signs	X	X	X	X	X	X	X				See Section 8.2.2 of the master protocol
Performance status (ECOG)	X	X	X	X	X	X	X				
SpO_2	X	As clinically indicated									
Laboratory and other investigations											
12-Lead ECG	X	X	As clinically indicated								See Section 8.2.3 of the master protocol
LVEF	X	As clinically indicated									See Section 8.2.3 of the master protocol
Troponin	X	As clinically indicated			X (Cycle 4 Day 1)	As clinically indicated					See Section 8.2.3 of the master protocol and Section 10.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Pregnancy test	X	X			X	X	X	X			See Section 8.2.5 of the master protocol and Section 10.2 of the master protocol
Hepatitis serology, CD4 counts and viral load	X[h]	As clinically indicated									See Section 10.2 of the master protocol and Section 10.7 of the master protocol
Hematology	X	X	X	X	X	X	X				See Section 10.2 of the master protocol
Coagulation	X	As clinically indicated									See Section 10.2 of the master protocol
Blood Chemistry	X	X	X	X	X	X	X				See Section 10.2 of the master protocol
Urinalysis[i]	X	X			X	X	X				See Section 10.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
T3, FT4, TSH & cortisol[j]	X				X	X	X				See Section 10.2
IMP											
SAR444245		X			X						
Pembrolizumab		X			X						
Hospitalization[k]		X									
AE/SAE assessment[l]	X	Continuously throughout treatment period					X				See Section 8.3 of the master protocol
Prior/Concomitant Meds	X	Continuously throughout treatment period									See Section 6.8 of the master protocol
First subsequent anti-cancer therapy						X	X	X	X	X	
Survival status										X	
Pharmacokinetic (PK) / Pharmacodynamic (PDy) / Immunogenicity assessments											
PK SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
ADA SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
PDy - Blood and tumor tissue collection[m,n]	See Biomarker flowchart in Section 1.4										

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Tumor assessment											
Brain imaging[o]	X										See Section 8.1 of the master protocol
CT/MRI[p]	X				X	X	X	X	X		See Section 8.1 of the master protocol

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. 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 first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator prior to IMP administration at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: a treatment cycle is 21 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

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 tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and 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 study.

e For Cycle 4 visits, please refer to PK flowchart in Section 1.5.

f C1D8 and/or C1D15 visits must be performed on site for the following participants only: 1) Participants scheduled to have blood draws for biomarker assessment and/or ADA on Day 8; 2) Participants who will receive IMP on Day 8 and Day 15. For all other participants, these 2 on-site visits may be done remotely as appropriate based on investigator's discretion per institutional standard and local regulations. If this is the case, this must be documented in the source document. Sponsor may decide to cancel safety assessment on C1D8 and C1D15 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 For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.7 of the master protocol).

i Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during Treatment Period and as clinically indicated.

j Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

k Only for participants who will participate in the intensive PK sample collection.

l AE/SAE assessment: 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 (1).

m If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

n Will not be done for participants enrolled in China.

o 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 as per protocol tumor assessment (TA) schedule. 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 4 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 have 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.

p CT/MRI: The initial tumor imaging will be performed within 28 days prior to C1D1. 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 of first IMP and 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, during treatment period until PD. Per the primary tumor assessment criteria, after the first documentation of response 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.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; AST=aspartate transaminase; ALT=alanine transaminase; C=Cycle; ANC=Absolute neutrophil count; AP=Alkaline phosphatase; BUN=Blood urea nitrogen; CRF=case report form; CRS=Cytokine release syndrome; CT=computed tomography; [redacted] D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FT4=free thyroxine; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; ICF=Informed consent form; IMP=investigational medicinal product; INR=international normalized ratio; LDH=Lactate hydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA= multigated acquisition; PD=progressive disease; [redacted]; PDy=pharmacodynamic; PK=pharmacokinetic; PR=partial response; PS=Performance Status; SpO2= oxygen saturation; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; T3=tri-iodothyronine; TSH=thyroid stimulating hormone; WBC=White blood cells.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHARTS

For participants who will undergo more intensive pharmacokinetic (PK) sampling, the schedule is shown in the flowchart in Section 1.5.1. Up to 30 participants enrolled across cohorts treated with SAR444245 + pembrolizumab (including Cohort A) will undergo more intensive PK sampling, up to 10 participants from China will undergo intensive PK sampling.

For all other participants, the PK sampling schedule is shown in the flowchart in Section 1.5.2.

1.5.1 Participants with more intensive PK sampling

Cycle	Cycle 1										Cycle 2, 3		Cycle 4									Cycles 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	D1									D8	D1		D1									D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	1	2	4	8	24	48	72	168	SOI	EOI	SOI	EOI	1	2	4	8	24	48	72	SOI	EOI	
SAR444245 PK sample ID	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08		P00[a]	P01[b]	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08	P00[a]	P01[b]	
Sample time window			±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h						±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h			
SAR444245 ADA sample ID[c]	AB00[a]									AB01	AB00[a]		AB00[a]									AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI),

b PK sample must be taken at EOI after flush.

c ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.

In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at EOI + 1 h, +2 h, +4 h, +8 h, +24 h, +48 h and +72 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end of resumed infusion and subsequent samples should be drawn at 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after end of resumed infusion (as per protocol).

ADA: anti-drug antibodies; EOI: End of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: Start of infusion.

1.5.2 All other participants

Cycle	Cycle 1				Cycles 2, 3. 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit
Day	D1			D8	D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	24	168	SOI	EOI	30 (±7) days after last IMP admin
SAR444245 PK sample		P01[b]	P06[c]			P01[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI)

b EOI samples = end of infusion samples. Must be taken at end of infusion precisely

c PK sample can be collected at any time during the second day of the cycle.

ADA: anti-drug antibodies, PK: pharmacokinetic: SOI: start of infusion; EOI: end of infusion

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to cohort with ESCC for the combination therapy with pembrolizumab.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models while anti-PD1 antibody prevents T cell suppression through the PD1/PD-L1 pathway. The combination of anti-PD1 treatment with SAR444245 was tested in a syngeneic mouse CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of CR and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the country approved labeling for detailed background information on pembrolizumab.

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD1 has been resolved (7). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (6, 8, 9, 10). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (13, 14, 15, 16, 17, 18, 19). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (7, 16, 18, 19, 20). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (18). Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab IB).

A summary of clinical trial data and the justification of the choice of pembrolizumab dose is provided in Section 4.3.2.

2.2.2 Rationale for ESCC and selected population (Cohort A)

Esophageal cancer is ranked as the sixth leading cause of cancer-related deaths. Although the incidence of adenocarcinoma is increasing in Western countries, esophageal squamous cell carcinoma (ESCC) is the major histology in Asian countries including Japan. Although driver gene mutations have not been detected in ESCC, the somatic mutation rate in ESCC is relatively high compared with other solid tumors (21). Up to the event of ICI, there was no agents that had shown clear efficacy in ESCC (22).

In the multi-cohort Phase 1b KEYNOTE-028 study, pembrolizumab monotherapy demonstrated promising antitumor activity in patients having heavily pre-treated esophageal carcinoma with PD-L1 ≥ 1%. Thirty-seven (45%) of patients had PD-L1 positive tumor, and ORR was 30% (28% in ESCC) with a median duration of response of 15 months (23). The subsequent phase II, single-arm KEYNOTE-180 study evaluated the activity of pembrolizumab monotherapy in patients with advanced, metastatic esophageal carcinoma who have failed two or more lines of therapy (24). PD-L1 expression, defined as a CPS of 10 or higher assessed by immunohistochemistry (IHC), was reported in 47.9%, and 52.1% of the 121 enrolled patients had ESCC. The ORR of the entire cohort was 9.9%, and numerically higher response rate was observed in those tumors with PD-L1 expression (ORR 13.8%) and ESCC (ORR 14.3%). The results were echoed in the phase II, single-arm Attraction-01/ONO-4538-07 study in which nivolumab monotherapy was given in Japanese patients with ESCC refractory or intolerant to standard treatments (25). PD-L1 expression was not required for study entry; the ORR was 17.2% and the responses were durable (26).

In the KEYNOTE-181 randomized Phase 3 study, pembrolizumab monotherapy was compared to the investigator's choice of chemotherapy in patients with advanced esophageal cancers, all histologies, who had received only one prior line of treatment. The primary objectives were overall survival (OS) in patients with PD-L1 CPS ≥10, ESCC and in the total population. Compared with investigator’s choice of chemotherapy, pembrolizumab monotherapy significantly improved OS in PD-L1 CPS ≥10 (9.3 versus 6.7 months, HR 0.69) and ESCC (8.2 versus 7.1 months, hazard ratio [HR] 0.78) but not in the total population (7.1 versus 7.1 months, HR 0.89). In addition, the ORRs were significantly higher with pembrolizumab than chemotherapy. It reached 21.5% in PD-L1 CPS ≥10 (versus 6.1% with chemotherapy; p = 0.0006), 16.7% in ESCC (versus 7.4% with chemotherapy; p = 0.0022), and 13.1% in total population (versus 6.7% with chemotherapy; p = 0.0037). In patients with ESCC and PD-L1 CPS ≥10, the ORR (22% versus 6%) and OS (10.3 months versus 6.7 months, HR=0.64) were significantly higher with pembrolizumab than chemotherapy. For the specific setting of patients with ESCC and PD-L1 CPS ≥10, the ORR of 22% (versus 6%) and OS of 10.3 months (versus 6.7 months, HR=0.64) were significantly higher with pembrolizumab than chemotherapy. Based on these data of Keynote-181 study, pembrolizumab received FDA approval for use in patients with recurrent or metastatic ESCC with a CPS ≥10 in the 2L setting (27). Nivolumab single agent is approved regardless of PDL1 expression in Japan and other Asian countries, and was also recently approved in the US and EU based on Attraction-3 data (28). Results from the randomized, international, double-blind KEYNOTE-590 study of 1L pembrolizumab + chemotherapy vs chemo alone in patients with locally advanced/unresectable or metastatic esophageal adenocarcinoma or ESCC or Siewert type 1 gastroesophageal junction cancer (GEJ) were reported at ESMO 2020 (29). At data cutoff, 749 patients (73% ESCC) were randomized. Median follow-up was 10.8 months. Pembro + chemo versus chemo was superior for OS in patients with ESCC CPS ≥10 (13.9 versus 8.8 months; HR 0.57), ESCC (12.6 versus 9.8 months; HR 0.72), CPS ≥10 (13.5 versus 9.4 months; HR 0.62), and all patients (median 12.4 versus 9.8 months; HR, 0.73). Confirmed ORR was 45.0% versus 29.3% (P <0.0001) in all patients, with median DoR of 8.3 versus 6.0 months. Safety profile was manageable but discontinuation rates from drug-related AEs was slightly higher in the combination arm (19% versus 12%). Pembrolizumab + chemotherapy may be the new SoC for this population in 1L, regardless of histology and PD-L1 expression. Nevertheless, >50% of patients do not respond, and some will relapse. In the proposed study, the antitumor activity of pembrolizumab when combined with SAR444245 will be evaluated in the population patients in 2-3L that will have failed or relapsed on an anti-PD-1/PD-L1.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Please refer to the master protocol for risk assessment for SAR444245, 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 when combined with pembrolizumab results from anticipated risks for SAR444245 and from the label information for Keytruda® (pembrolizumab), taking into account potential overlapping risks. The available safety data for pembrolizumab, along with proposed mitigation strategies are summarized below and also provided in Table 11.

2.3.1.1 Pembrolizumab

Pembrolizumab potentiates T-cell responses, including antitumor responses, through blockade of PD1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment (TME).

The use of pembrolizumab may cause IRRs (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, and hypersensitivity). Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated adverse events are designated as important identified risks for pembrolizumab (30).

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Among the immune-related AEs (irAEs) associated with pembrolizumab are: immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis, immune-related endocrinopathies, immune-related skin adverse reactions and other additional clinically significant, immune-related adverse reactions (reported in clinical studies or in post-marketing experience): uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, and myelitis.

Efficacy and safety data for pembrolizumab from patients ≥75 years are limited. In this population, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Please refer to the country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for pembrolizumab for more detailed information.

2.3.1.2 SAR444245 combined with pembrolizumab

Combining SAR444245 with pembrolizumab may lead to an increased frequency and/or severity of adverse events (AEs) related to immune activation or may lead to additional AEs related to immune system activation for each substance individually or may cause occurrences of qualitatively different AEs. Serious adverse drug reactions reported with agents known to increase immune activation include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction (see Section 2.3.1.1).

As both substances are biologic agents, they may have the propensity to induce infusion-related reactions that may have higher rate of occurrence and severity when SAR444245 with pembrolizumab are used in combination.

The maximum tolerated dose (MTD) of SAR444245 combined with the approved dosing of the anti PD-1 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.

2.3.2 Benefit assessment

More detailed information about the expected benefits of SAR444245 may be found in the master protocol, and the combination of SAR444245 and pembrolizumab are provided below.

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).

Immune checkpoint inhibitors are approved in most of the indications proposed to be tested in this study (please refer to Section 2.1 - Study Rationale): ESCC, gastric and gastroesophageal, HCC. In gastric cancer and ESCC, the main benefit of pembrolizumab is brought to patients with diseases that have a relatively high expression of PD-L1 (CPS ≥10). Combining SAR444245 to pembrolizumab is anticipated to expand to population responding to the anti-PD1 and to increase the quality of the response. Such effects have been demonstrated in the PIVOT-02 study for bempegaldesleukin combined with nivolumab in metastatic melanoma, achieving deep and durable responses with rates of CR of 34% and PFS (30.9 months) exceeding that reported in clinical trials for approved treatments (31). Objective responses were also documented in PDL1 negative cases (n=13), with an ORR of 39% and 3 patients achieving 100% reduction of target lesions, and 2 patients achieving CR. Echoing these results are those of the same combination in 1L metastatic urothelial carcinoma, an indication where response to immune checkpoint is linked to the level of expression of PD-L1. In this study, bempegaldesleulin when combined with nivolumab induced significant ORR with 17% CR, with ORR similar and PD-L1 negative (50%)

and PD-L1 positive (56%)(15), which contrast with data from Keynote-052 for pembrolizumab (32, 33). Combining SAR444245 with pembrolizumab is anticipated to bring benefit to patients with ESCC and GC/GEJ even in the context of low PD-L1 and could rescue patients who have progressed or relapsed following an anti-PD1/PD-L1.

2.3.3 Overall benefit: risk conclusion

More detailed information about the expected benefits of SAR444245 may be found in the master protocol.

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 pembrolizumab are justified by the anticipated benefits that may be afforded to participants with ESCC.

2.3.4 Benefit and risk assessment in the context of COVID-19 pandemic

Please refer to the master protocol for more details about risks related to the patient population, SAR444245 treatment, and study related activity.

In addition, the impact of PD-1 blockade therapy on Coronavirus disease 2019 (COVID-19) severity was also explored by 2 groups and did not find a clinically meaningful signal (34, 35).

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 1 - Objectives and endpoints

Objectives	Endpoints
Exploratory	
• [redacted]	[redacted] (36).

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Cohort A will assess SAR444245 adding on to pembrolizumab in participants with advanced unresectable or metastatic esophageal squamous cell carcinoma (ESCC), regardless of programmed cell death-ligand 1 (PD-L1) expression (any combined positive score [CPS]), who have received no more than two prior lines of treatment and have progressed after primary or secondary resistance to an anti-PD-1/PD-L1 based regimen (detailed in Section 5.1). Patients with known high MSI-H will not be eligible, but the determination of the MSI status will not be required for enrollment.

Please refer to the master protocol for a full description of the study design, and for details applicable to all therapy cohorts.

A graphical presentation of the substudy schema is shown in Figure 1. For treatment period, the completion of Cycle 35 is applicable for Cohort A.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with the anti-PD1 antibody pembrolizumab will result in a significant increase in the population experiencing an objective response.

The design of the 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 RECIST 1.1 for participants with advanced unresectable and metastatic ESCC.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB).
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications. And
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5- fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort A specific criteria.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply (in addition to the criteria listed in the master protocol):

Type of participant and disease characteristics

I 01. Histologically or cytologically confirmed diagnosis of esophageal cancer of the squamous cell carcinoma subtype.

I 02. Confirmed diagnosis at study entry of advanced unresectable or metastatic disease.

Note: *For participants in Cohort A*: Disease with any CPS scoring. No need for CPS determination at local laboratory.

I 03. MSI status: Participants must have either unknown MSI status or if MSI status is known, participants must have non-MSI-H disease to be eligible.

I 04. Prior anticancer therapy: Participants should have received at least one but no more than 2 prior lines of treatment, including an anti-PD-1/PDL-1 containing regimen and have progressed after a primary or secondary resistance to an anti-PD-1/PDL-1.

Note: For Cohorts A:

Primary resistance is defined as a patient who has experienced progressive disease (PD) or SD lasting <6 months of initiation of PD-1/PD-L1 inhibitor-based treatment and who received at least 6 weeks of the PD1/PD-L1. Radiographic confirmation of the PD must be documented after a minimum of 4 weeks after the initial identification of progression, unless: i) investigator confirms clinical progression/ deterioration attributed to PD, or ii) the first radiographic assessment indicated critical tumor growth by imaging (size or location).

Or

Secondary resistance: patients must have experienced PD, either during or within 3 months of discontinuing treatment with anti-PD1-based therapy, occurring after previous clear benefit (any complete [CR] or partial response [PR]), or after previous stable disease (SD) >6 months. No requirement for radiographic confirmation of progression.

An anti-PD1/PD-L1 containing regimen is defined as either an anti-PD1/PD-L1 monotherapy, or an anti-PD1/PD-L1 agent administered in the same cycle as another systemic anticancer therapy. If PD1/PD-L1 was used beyond initial radiological progression while continuing to use the same PD1/PD-L1 agent used before PD, it's still considered as the same regimen. The site's study team must have reviewed previous tumor assessments (including screening tumor imaging) to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the anti-PD1/PD-L1 containing regimen.

I 05. Provision of tumor tissue:

- **Mandatory baseline biopsy** for participants in **Cohort A**: minimum 5 slides with 4-5 micron thickness for the first 20 participants who have signed ICF (excluding screen failure participants), minimum 10 slides with 4-5 micron thickness for subsequent participants. Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- **Optional on-treatment biopsy** for Cohort A per Investigator's discretion and evaluation.
- 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.

5.2 EXCLUSION CRITERIA

Please refer to the master protocol.

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

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

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

For study treatment duration, completion of Cycle 35 is applicable for Cohort A.

Dosing sequence: [redacted]

In addition, if a participant has immune unconfirmed progression of disease (iUPD) and is clinically stable, it is at the discretion of the Investigator to continue treating the participant with the assigned treatment per protocol until progression of disease is confirmed (iCPD) at least 4 weeks, but no longer than 8 weeks from the date of the scan suggesting progression of disease (Section 10.9).

6.1.1 Investigational medicinal product (IMP)

Investigation medicinal product is defined as SAR444245 and pembrolizumab administered in combination as described in Section 4. Details of each IMP component to be administered are shown in Table 2.

Preparation and administration of IMP are detailed in the pharmacy manual.
Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 2 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	100 mg/vial
Dosage level(s)[a]	24 µg/kg Q3W	200 mg Q3W
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	See master protocol	IMP
Packaging and labeling	See master protocol	Supplied in single dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.
Current/Former name(s) or alias(es)	See master protocol	Keytruda

a See master protocol.

6.1.2 Non-investigational medicinal products

Please refer to the master protocol.

In case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, SAR444245 premedication no longer needs to be administered.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications for SAR444245 are permitted according to the guidelines described in this section. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

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, Day 1 should be delayed for all IMPs) is permitted in case of treatment-emergent adverse event (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.

In participants who have SAR444245 dose reduction due to SAR444245 related Grade ≥3 treatment-related adverse events (TRAEs), SAR444245 dose may be re-escalated to ■ µg/kg if:

- no SAR444245 related Grade ≥3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND
- both Investigator and Sponsor agree that the participant has clinical benefit.

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 of the master protocol 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 all IMP components are permanently discontinued, it is full permanent discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.5.2 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 the next dose after recovery from the toxicity as described in Section 6.5.3 and Section 6.5.4. After cycle is delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline.

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 delay, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for the delay should be documented in the participant's study record.

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

Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 3-8) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline

The dose of SAR444245 should be reduced to [redacted] µg/kg (with the exception of lymphocytopenia which is directly associated with SAR444245 mode-of-action and does not require dose reduction) in cases of:

- First occurrence of Grade 3 TRAE that does not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 TRAE of any duration.
- Grade 4 TRAE.
- First occurrence of Grade 3 laboratory abnormality that are clinically significant per Section 10.3.1 of the master protocol. and that do not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 clinically significant laboratory abnormality of any duration.
- Grade 4 laboratory abnormalities that are clinically significant.

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

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

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.

Recommended guidelines for the management of specific adverse events including irAE, CRS, Vascular Leak Syndrome (VLS) and Infusion-related reactions (IRR) are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as adverse events of special interest (AESIs), depending on grading according to National Cancer Institute- Common Terminology Criteria for Adverse Event (NCI-CTCAE) V5.0 (see Section 8.3.8 of the master protocol). In case a specific adverse event meets the AESI definition it must be documented in the e-CRF.

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol 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.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 3.

After an infusion-related reaction due to pembrolizumab infusion (Grade 3 or Grade 4), the SAR444245 infusion will be delayed and can be administered after resolution of symptoms. The Investigator should discuss with the Sponsor's Medical Monitor if the SAR444245 infusion needs to be delayed more than 1 day.

Guidelines for the management of SAR444245 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, please see Section 6.1.2.1 of the master protocol.

Table 3 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - Epinephrine*, - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics, - Oxygen, - Pressors, - Corticosteroids. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Table 4 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE 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 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	SAR444245 infusion should be interrupted if applicable. If symptoms resolve within 1 hour of interrupting 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 should be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. The next infusion should be given 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 (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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.
Grade 4 Life-threatening; pressor or ventilator support indicated	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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 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; NCI = National Cancer Institute; NSAIDs: nonsteroidal anti-inflammatory drugs.

6.5.4.2 Anaphylaxis

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

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) (37, 38, 39).

6.5.4.3 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 V5.0 and managed according to institutional standards.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (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 C-reactive protein (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 according to severity grading are provided in Table 5. ASTCT CRS consensus grading scale is provided in Section 10.11 of the master protocol.

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

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] 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 participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during 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. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement,

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
	hypotension, or participants 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. SAR444245 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.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS grade 3, SAR444245 should be temporarily cycle delayed, and subsequent treatment should be resumed only when symptoms have resolved or improved to Grade 1 at [redacted]µg/kg or permanently discontinued, as clinically indicated. If CRS Grade 4, SAR444245 should be permanently discontinued as clinically indicated. If CRS Grade 3 or Grade 4, IV corticosteroids should be initiated (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, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants 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 should be discussed with clinical site specialists

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b 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.

c 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.

d 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: 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; IL = Interleukin; IMP=investigational medicinal product; IV = Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.5.4.4 Immune-related adverse events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. IrAEs are thought to be caused by unrestrained cellular immune responses directed at the normal host tissues. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing pembrolizumab clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care.

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 severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 6. Of note, when study interventions are administered in combination, 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.

The CTCAE V5.0 must be used to grade the severity of AEs.

When pembrolizumab can be restarted, it should be administered at the initial planned dose and schedule as no modification is allowed:

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 6, the combination of SAR444245 or pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 6 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab and SAR444245 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab and SAR444245 have been withheld, pembrolizumab and SAR444245 may be resumed after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold[a]	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue[b]		
Diarrhea/Colitis	Grade 2 or 3	Withhold[a]	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis 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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		
AST or ALT elevation or Increased Bilirubin	Grade 2[c]	Withhold[a]	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
	Grade 3[d] or 4[e]	Permanently discontinue[b]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a,f]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2 Grade 3 or 4	Withhold[a] Withhold[a] or permanently discontinue[b,f]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
Hyperthyroidism	Grade 2 Grade 3 or 4	Continue Withhold[a] or permanently discontinue[b,f]	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Neurological Toxicities	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
All Other irAEs	Persistent Grade 2 Grade 3 Recurrent Grade 3 or Grade 4	Withhold[a] Withhold[a] or discontinue based on the event[g] Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up

a SAR444245 to be withheld plus pembrolizumab to be withheld corresponds to "cycle delay".
b Permanently discontinuation of full study treatment.
c AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal.
d AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal.
e AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.
f The decision to withhold or permanently discontinue pembrolizumab and SAR444245 is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab and SAR444245 may be resumed.
g Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).
AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

6.5.4.5 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 10.11 of the master protocol). Recommendations for ICANS) management mainly include the use of 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 SAR444245 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.	SAR444245[a] should be delayed. Treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted] µg/kg 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	If Grade 3 ICANS, SAR444245 should be delayed. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor.

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
EEG that resolve with intervention. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 4 ICANS, SAR444245 should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 5 in Section 6.5.4.3. 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, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants 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 clinical specialists should be involved whenever indicated.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual
Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; ICANS= Immune effector cell associated neurotoxicity syndrome; ICE= Immune Effector Cell-Associated Encephalopathy; IV = Intravenous.

6.5.4.6 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 (40).

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

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	SAR444245 should be delayed. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. 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. In participants 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 Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AKI= acute kidney injury; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; MW= molecular weight; NCI = National Cancer Institute; VLS= vascular leak syndrome.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for definition and treatment of SAR444245 overdose.

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol and Section 1.3.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

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

Please refer to the master protocol for RECIST 1.1.

[redacted]

8.2 SAFETY ASSESSMENTS

Please refer to the master protocol.

In addition, combining SAR444245 with other anticancer therapies may increase the frequency and severity of immune-related adverse events related to other anticancer therapies. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level will be monitored.

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

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information.

Please refer to the master protocol for AEs and serious adverse events (SAEs) collection. For participants in Cohort A irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

For pembrolizumab, SAEs that are considered expected will be specified in the reference safety information (country-approved product labeling for pembrolizumab).

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Please refer to the master protocol.

In addition, symptomatic or asymptomatic overdose with pembrolizumab are described as below:

- An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

The plan is to treat approximately 40 participants in Cohort A.

Table 9 lists estimated ORR and 90% exact confidence intervals (CIs) by number of responders from a sample size of 40 participants treated.

Table 9 - Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
2	5% (0.9% - 14.9%)
4	10% (3.5% - 21.4%)
6	15% (6.7% - 27.5%)
8	20% (10.4% - 33.2%)
10	25% (14.2% - 38.7%)
12	30% (18.3% - 44.0%)
14	35% (22.6% - 49.2%)

CI: confidence interval; N=number.

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 cohort.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

Please refer to the master protocol.

9.4.3 Secondary endpoint(s)

Please refer to the master protocol.

9.4.4 Tertiary/exploratory endpoint(s)

[redacted]

9.4.4.1 Exploratory antitumor indicators

[redacted]

9.4.5 Other safety analysis

Please refer to the master protocol.

9.4.6 Other analysis

Please refer to the master protocol.

9.5 INTERIM ANALYSES

Please refer to the master protocol.

If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5%) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

Please refer to the master protocol.

10.1.2 Financial disclosure

Please refer to the master protocol.

10.1.3 Informed consent process

Please refer to the master protocol.

10.1.4 Data protection

Please refer to the master protocol.

10.1.5 Committees structure

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

Please refer to the master protocol.

10.1.7 Data quality assurance

Please refer to the master protocol.

10.1.8 Source documents

Please refer to the master protocol.

10.1.9 Study and site start and closure

Please refer to the master protocol.

10.1.10 Publication policy

Please refer to the master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort A specific evaluations are presented in Table 10.

Table 10 - Protocol-required laboratory tests

Laboratory tests	Parameters
Endocrine function tests[a]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

NOTES :

a Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT in cohorts receiving pembrolizumab. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol.

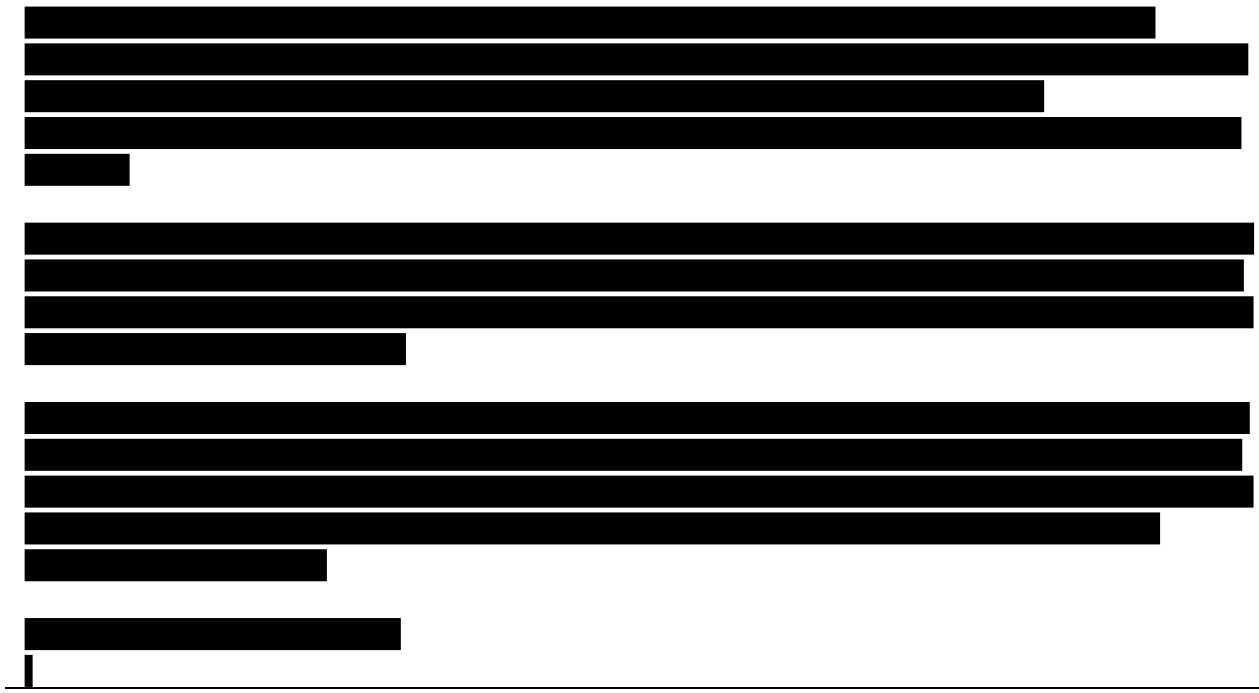
10.8 APPENDIX 8: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1

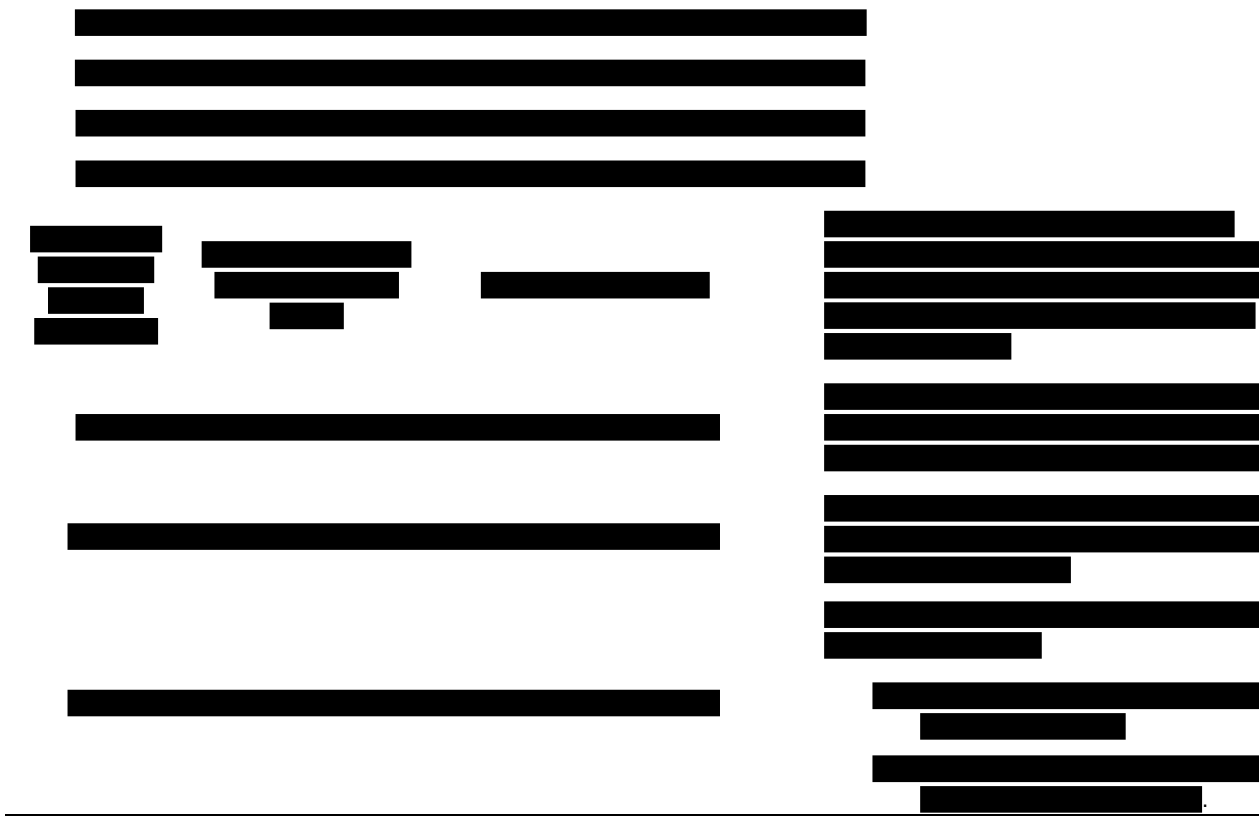
Please refer to the master protocol.

10.9 APPENDIX 9: [redacted]

[redacted]

New lesions:





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. 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: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Please refer to the master protocol.

10.11 APPENDIX 11: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245, available information about pembrolizumab is shown in Table 11.

Table 11 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion associated reactions are provided in Table 3.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.
Hepatotoxicity	Pembrolizumab Hepatitis occurred in 0.8% of patients, including Grade 2, 3 or 4 cases in 0.1%, 0.5% and 0.1% patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.6 months (range 8 days to 21.4 months). The median duration was 1.1 months (range 1 day to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 0.3% patients. Hepatitis resolved in 36 patients.	Dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Table 6.
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 6.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 6.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 6.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.8 of the master protocol.

10.12 APPENDIX 12: ASTCT ASSESSMENT FOR ICANS AND CRS

Please refer to the master protocol.

10.13 APPENDIX 13: ABBREVIATIONS

AESIs: adverse events of special interest
ASTCT: American Society for Transplantation and Cellular Therapy
CPS: combined positive score
CR: complete response
[redacted]
e-CRF: electronic case report form
EOT: end of treatment
ESCC: esophageal squamous cell carcinoma
ICANS: immune Cell-Associated Neurotoxicity Syndrome
ICU: intensive care unit
[redacted]
IRR: infusion-related reactions
MSI-H: microsatellite instability
NCI-CTCAE: National Cancer Institute- Common Terminology Criteria for Adverse Event
NHP: non-human primate
[redacted]
PD1: programmed cell death protein 1
[redacted]
PK: pharmacokinetic
SAEs: serious adverse events
TEAE: treatment-emergent adverse event
TIL: tumor infiltrating lymphocytes
VLS: Vascular Leak Syndrome

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

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

10.14.1 Amended protocol 01 (30 August 2021)

This amended protocol (Amendment 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 overall rationale for the amendment is to include stopping rules for futility and update the rules for dose modification in case of treatment-related adverse events (TRAEs) for Cohort A in substudy 01.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	I04 has been revised from "Participants should have received at least but no more than 2 prior lines of treatment…" to "Participants should have received at least one but no more than 2 prior lines of treatment…".	For correction.
	In I06, "- less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "-less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment".	Harmonization per program level approach.
Section 6.5.1 General rules	The following sentence has been deleted "Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.", and the following sentences have been added "In participants who have SAR444245 dose reduction due to SAR444245 related Grade ⩾3 TRAEs, SAR444245 dose may be re-escalated to [redacted] µg/kg if: •no SAR444245 related Grade ⩾3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND •both Investigator and Sponsor agree that the participant has clinical benefit.".	For clarification of how dose will be reduced and re-escalated for participants who experience any Grade ⩾3 TRAEs.
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following sentence "Participants who experience Grade ⩾3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) will be required to temporarily delay the IMP, unless specified	For consistency and clarity.

Section # and Name	Description of Change	Brief Rationale
	otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy." has been changed to "Participants who experience Grade ⩾3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 3-8) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline". Dose reduction rules have added, and the following sentence has been deleted "Dose reduction for SAR444245 from ■µg/kg to ■ µg/kg (or another lower recommended dose) may be decided when specified in the protocol or following discussions with the Sponsor." .	
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 4 under Grade 3 and Grade 4, "prematurely" has been removed from "prematurely permanently discontinued".	For clarity.
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 5 under Grade 3, the following sentence was deleted "If subsequent administration is tolerated, increasing the SAR444245 dose to ■µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor".	For consistency.
Section 9.5 Interim analyses	The following sentences have been added "If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5%) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.".	To include stopping rules for futility.

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Signature Page for VV-CLIN-0617848 v3.0
act16902-16-1-1-amended-protocol02-substudy01

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 02 (SUBSTUDY 02)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants with advanced and metastatic gastric cancer or gastro-esophageal junction adenocarcinoma**
Protocol number:	**ACT16902-S02**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab for the treatment of participants with gastric cancer or gastro-esophageal junction adenocarcinoma**
Study phase:	**Phase 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:	156424
EudraCT:	2021-002181-41
NCT:	NCT05104567
WHO:	U1111-1251-4981

Date: 12-Jan-2022 Total number of pages: 73

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02 (Substudy 02)	All	12 January 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 02)	All	30 August 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 02)		20 July 2021, version 1 (electronic 1.0)

Amended protocol 02 (12 January 2022)

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 main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Belgian, Italian, German (Federal Institute for Drugs and Medical Devices [BfArM]), and South Korean Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA is provided for this substudy with procedures taken from the master protocol. And the previous footnote a for endocrine function tests has been renumbered as footnote j in the current document.	Regulatory Authorities (BfArM) request.
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessment of any potential cardiotoxity.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Patient-reported outcome assessment have been added.	To assess patient-reported experience of treatment [redacted] in an exploratory endpoint.
3 Objective and endpoints	Exploratory objective and endpoints for Patient-reported outcomes have been added.	
8.10 Patient-reported outcomes (PRO)	New section added.	
9.4.4.2 Patient-reported outcomes	Analysis for PRO endpoints has been added.	
1.4 Biomarker flowchart	A complete Table of biomarker flowchart is provided for this substudy with biomarker sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.
1.5 Pharmacokinetic flowcharts	A complete Table of pharmacokinetic (PK) flowcharts are provided for this substudy with PK sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.
5.1 Inclusion criteria	For I07, "for whom available SOC should not be in their best interest" has been added.	For clarity.
5.1 Inclusion criteria, 10.7 Appendix 7: Country-specific requirements	South Korea specific requirements has been added for I07 and I08, to clarify that Korean patients will not be enrolled in Cohort B1 or Cohort B2 to receive SAR444245 + pembrolizumab as 1st or 2nd line (L) treatment neither in Cohort B3 to receive SAR444245 + pembrolizumab as 2nd L.	Regulatory Authorities request.

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Cohort-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants with advanced and metastatic gastric cancer or gastro-esophageal junction adenocarcinoma

Brief title: A study of SAR444245 combined with pembrolizumab for the treatment of participants with gastric cancer or gastro-esophageal junction adenocarcinoma

Rationale:

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 CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of complete responses (CR) and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with an anti-PD1 antibody.

High-level microsatellite instability (MSI-H) has been associated with better clinical outcomes in metastatic gastroesophageal cancer participants treated by PD1/PD-L1-based regimens but the prevalence of MSI-H in metastatic gastric cancer is low (~10%). Hence, the proposed study would focus on non MSI-H tumors with a large unmet need to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with the anti-PD1 antibody pembrolizumab will result in a significant increase in the percentage of patients experiencing an objective response in the setting of advanced unresectable or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma (GC/GEJ), especially with low PD-L1 expression or after progression on prior PD1/PD-L1-based regimens.

Objectives and endpoints

Please refer to the master protocol.

Overall design:

Please refer to the master protocol.

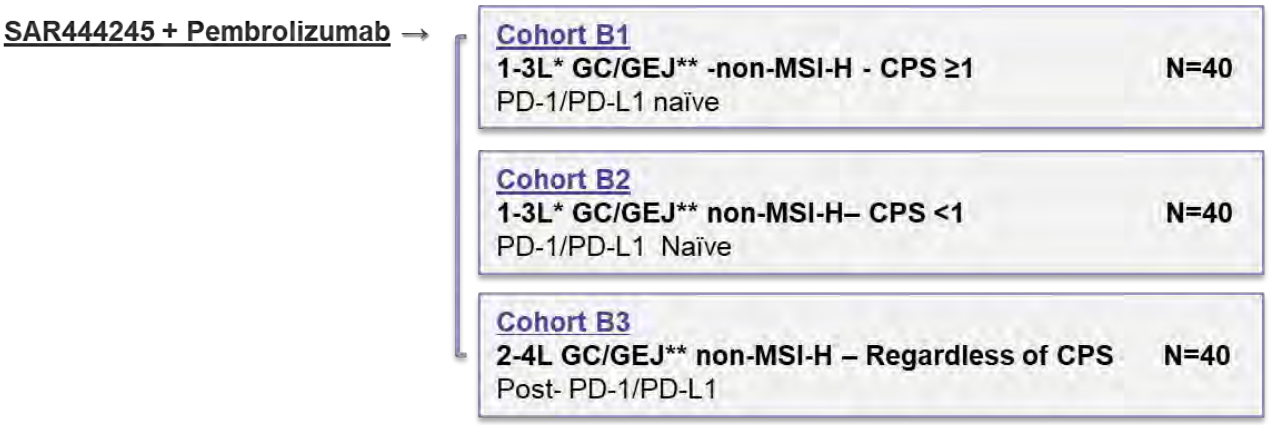
Brief summary:

Cohorts B1, B2 and *B3* will assess SAR444245 adding on to pembrolizumab in participants with advanced unresectable or metastatic GC or Siewert Type 2 & 3 GEJ and for whom receiving standard of care (SOC) is not of best interest (for example, participants who are not eligible, cannot tolerate, decline to receive, or have no access to such treatment) or where no SOC is established. MSI-H cases will not be eligible. HER2 + cases will not be eligible unless they have progressed on a trastuzumab-based treatment.

- *Cohorts B1 & B2* participants must not have received more than two prior lines of treatment that did not include an anti-PD1/PD-L1-based regimen. Participants will be assigned to one of these 2 cohorts according to the level of PD-L1 expression at baseline using the CPS as follow:
  - *Cohort B1:* participants with CPS ≥1 GC/GEJ
  - *Cohort B2*: participants with CPS <1 GC/GEJ
- *Cohort B3* participants are eligible regardless of the disease CPS status and must have received at least one and no more than three prior lines of treatment and have progressed after primary or secondary resistance to an anti-PD1/PD-L1-based regimen (detailed in Section 5.1).

A graphical presentation of the substudy schema is shown Figure 1.

Figure 1 - Overall study schema - Substudy 02



* In 1L, when receiving standard of care (SOC) is not in the best interest of the participant

** non-MSI-H and HER2 negative (or HER2 positive if progression is noted on trastuzumab based therapy)

Abbreviations: 1-3L: first-line to third-line; 2-4L: second- to fourth-line; CPS: combined positive score; GC: gastric cancer; GEJ: gastro-esophageal junction adenocarcinoma; MSI-H: high-level microsatellite instability; N=number; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in each of Cohorts B1, B2, and B3.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration for a participant in Cohorts B1, B2, and B3. For treatment period, the completion of Cycle 35 is applicable for all 3 cohorts.

Study intervention(s)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab

- **Formulation**: Keytruda® (pembrolizumab) as 100 mg/4 mL (25 mg/mL) solution in single-dose vials
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle for **up to 35 cycles**.

Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

SAR444245

SAR444245 formulation, route of administration, and dose regimen as described in the master protocol. Treatment duration for Cohorts B1, B2, and B3 is up to 35 cycles.

Noninvestigational medicinal products

Please refer to the master protocol.

After 4 cycles, in case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, premedication no longer needs to be administered.

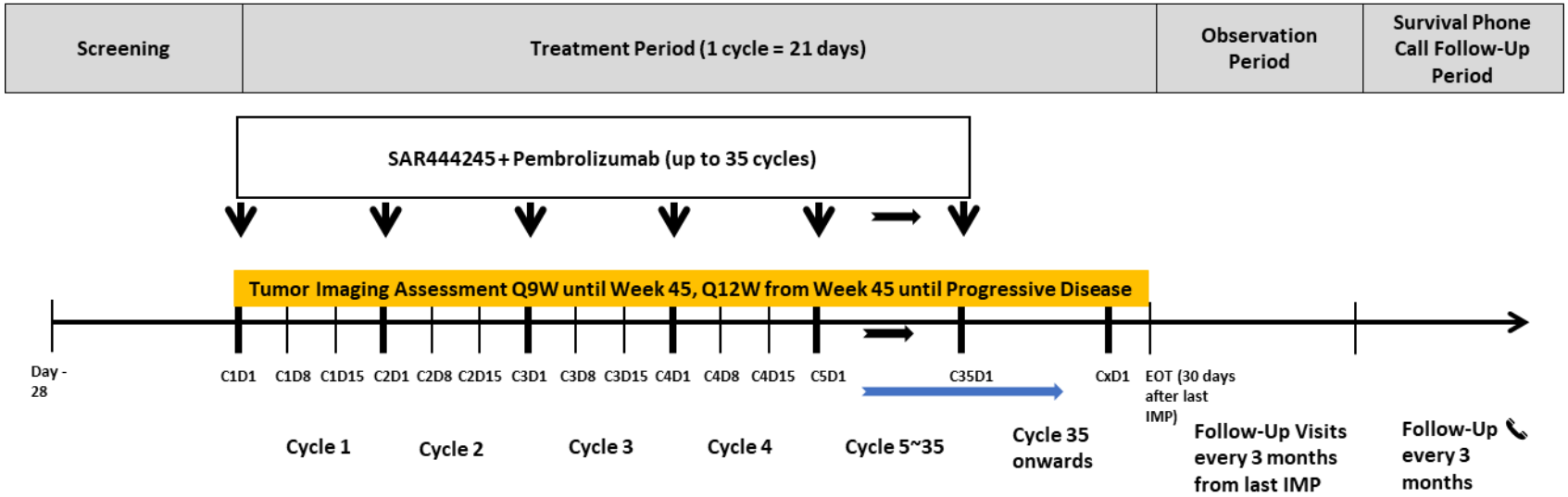
Statistical considerations:

Please refer to master protocol.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 2 - Graphical study design - Cohorts B1, B2, and B3



C=Study cycle; D=Study day; EOT=end of treatment; IMP=Investigational medicinal product; Q9W=every 9 weeks; Q12W=every 12 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Informed consent	X										
Inclusion and exclusion criteria	X										
IRT contact	X	X			X	X					
Demography, medical/surgical and disease history	X										See Section 8 of the master protocol
Body Weight / Height[g]	X	X	X	X	X	X	X				
Full physical examination	X					X					See Section 8.2.1 of the master protocol
Directed Physical examination		X	X	X	X		X				See Section 8.2.1 of the master protocol
Vital Signs	X	X	X	X	X	X	X				See Section 8.2.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Performance status (ECOG)	X	X	X	X	X	X	X				
SpO_2	X	As clinically indicated									
Laboratory and other investigations											
12-Lead ECG	X	X	As clinically indicated								See Section 8.2.3 of the master protocol
LVEF	X	As clinically indicated									See Section 8.2.3 of the master protocol
Troponin	X	As clinically indicated			X (Cycle 4 Day 1)	As clinically indicated					See Section 8.2.3 of the master protocol and Section 10.2 of the master protocol
Pregnancy test	X	X			X	X	X	X			See Section 8.2.5 of the master protocol and Section 10.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
Hepatitis serology, CD4 counts and viral load	X[h]	As clinically indicated									See Section 10.2 of the master protocol and Section 10.7 of the master protocol
Hematology	X	X	X	X	X	X	X				See Section 10.2 of the master protocol
Coagulation	X	As clinically indicated									See Section 10.2 of the master protocol
Blood Chemistry	X	X	X	X	X	X	X				See Section 10.2 of the master protocol
Urinalysis[i]	X	X			X	X	X				See Section 10.2 of the master protocol
T3, FT4, TSH & cortisol[j]	X				X	X	X				See Section 10.2
IMP											
SAR444245		X			X						
Pembrolizumab		X			X						
Hospitalization[k]		X									
AE/SAE assessment[l]	X	Continuously throughout treatment period					X				See Section 8.3 of

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ± 7 days**	**Every 3 months+/- 14 days**	
											the master protocol
Prior/Concomitant Meds	X	Continuously throughout treatment period									See Section 6.8 of the master protocol
First subsequent anti-cancer therapy						X	X	X	X	X	
Survival status										X	
Pharmacokinetic (PK) / Pharmacodynamic (PDy) / Immunogenicity assessments											
PK SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
ADA SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
PDy - Blood and tumor tissue collection[m,n]	See Biomarker flowchart in Section 1.4										
Tumor assessment											
Brain imaging[o]	X										See Section 8.1 of the master protocol
CT/MRI[p]	X				X	X	X	X	X		See Section 8.1 of the master protocol
Patient-reported outcome assessment											
[redacted]	[redacted]										[redacted]

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. 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 first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator prior to IMP administration at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: a treatment cycle is 21 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

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 tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and 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 study.

e For Cycle 4 visits, please refer to PK flowchart in Section 1.5.

f C1D8 and/or C1D15 visits must be performed on site for the following participants only: 1) Participants scheduled to have blood draws for biomarker assessment and/or ADA on Day 8; 2) Participants who will receive IMP on Day 8 and Day 15. For all other participants, these 2 on-site visits may be done remotely as appropriate based on investigator's discretion per institutional standard and local regulations. If this is the case, this must be documented in the source document. Sponsor may decide to cancel safety assessment on C1D8 and C1D15 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 For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.7 of the master protocol).

i Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during Treatment Period and as clinically indicated.

j Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated

k Only for participants who will participate in the intensive PK sample collection.

l AE/SAE assessment: 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 (1).

m If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

n Will not be done for participants enrolled in China.

o 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 as per protocol tumor assessment (TA) schedule. 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 4 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 have 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.

p CT/MRI: The initial tumor imaging will be performed within 28 days prior to C1D1. 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 of first IMP and 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, during treatment period until PD. Per the primary tumor assessment criteria, after the first documentation of response 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.

q [redacted]

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; AST=aspartate transaminase; ALT=alanine transaminase; C=Cycle; ANC=Absolute neutrophil count; AP=Alkaline phosphatase; BUN=Blood urea nitrogen; CRF=case report form; CRS=Cytokine release syndrome; CT=computed tomography; [redacted] D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FT4=free thyroxine; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; ICF=Informed consent form; IMP=investigational medicinal product; INR=international normalized ratio; LDH=Lactate hydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA= multigated acquisition; PD=progressive disease; [redacted]; PDy=pharmacodynamic; PK=pharmacokinetic; [redacted]; PR=partial response; PS=Performance Status; SpO2= oxygen saturation; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; T3=tri-iodothyronine; TSH=thyroid stimulating hormone; WBC=White blood cells.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHARTS

For participants who will undergo more intensive pharmacokinetic (PK) sampling, the schedule is shown in the flowchart in Section 1.5.1. Up to 30 participants enrolled across cohorts treated with SAR444245 + pembrolizumab (including Cohorts B1, B2, and B3) will undergo more intensive PK sampling, up to 10 participants from China will undergo more intensive PK sampling.

For all other participants, the PK sampling schedule is shown in the flowchart in Section 1.5.2.

1.5.1 Participants with more intensive PK sampling

Cycle	Cycle 1										Cycle 2, 3		Cycle 4									Cycles 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	D1									D8	D1		D1									D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	1	2	4	8	24	48	72	168	SOI	EOI	SOI	EOI	1	2	4	8	24	48	72	SOI	EOI	
SAR444245 PK sample ID	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08		P00[a]	P01[b]	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08	P00[a]	P01[b]	
Sample time window			±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h						±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h			
SAR444245 ADA sample ID[c]	AB00[a]									AB01	AB00[a]		AB00[a]									AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI),

b PK sample must be taken at EOI after flush.

c ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.

In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at EOI + 1 h, +2 h, +4 h, +8 h, +24 h, +48 h and +72 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end of resumed infusion and subsequent samples should be drawn at 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after end of resumed infusion (as per protocol).

ADA: anti-drug antibodies; EOI: End of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: Start of infusion.

1.5.2 All other participants

Cycle	Cycle 1				Cycles 2, 3. 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit
Day	D1			D8	D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	24	168	SOI	EOI	30 (±7) days after last IMP admin
SAR444245 PK sample		P01[b]	P06[c]			P01[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI)
b EOI samples = end of infusion samples. Must be taken at end of infusion precisely
c PK sample can be collected at any time during the second day of the cycle.

ADA: anti-drug antibodies, PK: pharmacokinetic: SOI: start of infusion; EOI: end of infusion

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to cohorts with advanced unresectable or metastatic GC or Siewert Type 2 & 3 GEJ for the combination therapy with pembrolizumab.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models while anti programmed cell death-1 (anti-PD1) antibody prevents T cell suppression through the PD1/PD-L1 pathway. The combination of anti-PD1 treatment with SAR444245 was tested in a syngeneic mouse CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of CR and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the country approved labeling for detailed background information on pembrolizumab.

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD1 has been resolved (7). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (6, 8, 9, 10). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (13, 14, 15, 16, 17, 18, 19). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (7, 16, 18, 19, 20). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (18). Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab IB).

A summary of clinical trial data and the justification of the choice of pembrolizumab dose is provided in Section 4.3.2.

2.2.2 Rationale for GC/GEJ and selected populations (Cohorts B1, B2 and B3)

Gastric cancer (GC) is an important health problem, being the 5th most common cancer and the 3rd leading cause of cancer death worldwide. In 2018, over 1 million new cases of GC (5.7% among all cancer cases diagnosed) were diagnosed with an estimated 782 685 deaths related to GC. It accounts for 8.2% of all deaths from cancers in 2018 (21). In the United States, 27 600 new cases of GC and 11,010 related death are estimated in 2020 (22). Eastern Asia is a high-risk area

of GC. GC is the second most common cancer in China, following lung cancer and the mortality is the third highest (after lung and liver cancers) (21). The GEJ is anatomically separated from GC, but their pathological types, molecular types, genetic variations, and therapeutic approaches are similar (23). First-line chemotherapy most commonly comprises platinum and fluoropyrimidine, which extends overall survival (OS) by approximately 6.7 months (23). Disease progression after 1L chemotherapy is common and 2L treatment options include docetaxel, paclitaxel, irinotecan as a single agent or in combination therapy. In addition, trastuzumab for patients with HER-2 positive disease and anti-VEGFR2 monoclonal antibody ramucirumab are also approved as 2L therapies. Pembrolizumab, was approved by FDA in 2017 for its use in advanced, recurrent GC expressing PD-L1 (CPS ≥1), after two prior lines of treatment, which was based on ORR from the phase II KEYNOTE-059 clinical trial (24). The phase II trial ONO4538 and phase III trial ATTRACTION-2 revealed that nivolumab administration to heavily pre-treated GC patients is associated with improved OS, compared to patients treated with placebo (25). These results led to the approval of nivolumab in Japan for the treatment of advanced stage GC patients progressing after standard systemic cytotoxic therapy, regardless of the PD-L1 status. In this study, PDL1 expression in tumor cells was documented only retrospectively using TPS. The so called combined positive score (CPS), which takes into account the PD-L1 positivity on cancer and infiltrating immune cells, has been shown to be a better scoring method than the percentage of PD-L1+ tumor. In the 2L KEYNOTE-061 trial, treatment with pembrolizumab failed to show a significant survival benefit when compared to paclitaxel, however, patients with higher PD-L1 levels by CPS showed a trend towards better survival (26). Indeed, the overall survival of GC patients treated with pembrolizumab was longer than that of patients under chemotherapy in CPS ≥10, which could not be recapitulated with a CPS ≥1. There were similar findings in the KEYNOTE-062 randomized trial in the 1L setting, where only patients with CPS ≥1 disease were randomized to receive either pembrolizumab alone or in combination with chemotherapy, or chemotherapy alone. (pembrolizumab ± chemo versus chemotherapy). In this trial, neither the pembrolizumab alone nor pembrolizumab combined with chemo improved OS in the CPS ≥1 population, but pembrolizumab with or without chemo had comparable survival and pembrolizumab was found noninferior to chemotherapy in that same population. Unfortunately, this noninferiority was associated with significantly worst outcome in terms of ORR (15%) and progression-free survival (PFS) (2 months) when compared to chemo alone (ORR 37% and PFS 6.4 months). However, in patients with tumors having a CPS ≥10, pembrolizumab alone (and not pembrolizumab with chemotherapy) was associated with an impressive OS (median OS, 17.4 months [HR, 0.69; 95% CI, 0.49-0.97]) which unfortunately had no α attributed and thus could not be considered a statistically significant result (27). As both KEYNOTE-061 and KEYNOTE -062 were negative studies, pembrolizumab is therefore not approved in the 1 & 2L settings but remained approved after two prior lines of treatment in CPS ≥1.

Very recently, the positive results of two randomized trial for nivolumab combined with oxaliplatin-based chemotherapy regimens in the 1L setting were disclosed. The CheckMate-649 trial enrolled GC/GEJC/EAC patients regardless of CPS with a primary endpoint for OS in the CPS≥5 (28). The study demonstrated superior OS (14.4 versus 11.1 months, HR 0.71; p<0.0001) with 29% reduction in risk of death, and a 3.3 months improvement in median OS with nivolumab plus chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥5. This survival benefit was extended to all study population including PD-L1 CPS≥1, however the CPS <5 may have been underrepresented. In the ATTRACTION-4 study (29), Asian patients with GC/GEJ were enrolled regardless of the PD-L1 status of their disease. PFS (interim analysis) was

significantly improved (median PFS, 10.5 versus 8.3 months, HR 0.68; p = 0.0007) in the experimental arm however, there was no statistically significant improvement in OS, which might have been due to 2L treatment containing immune checkpoint inhibitors in the control arm. Nivolumab plus chemo represents a new potential 1st line standard treatment for patients with advanced GC/GEJ cancers.

Indeed, in non-MSI-H GC/GEJ cancer, the KEYNOTE and CheckMate studies highlights the importance of PD-L1 expression on the response and potential benefit in OS, even in the absence of chemotherapy. Combining SAR444245 with an immune checkpoint inhibitor may allow to expand the population of patients who may benefit from an ICI, especially in the context of low or no PD-L1 expression. Cohort B1 and B2 aims to bring evidences that the combination of SAR444245 with pembrolizumab can have a meaningful increase in the ORR induced by pembrolizumab alone in ICI-naïve patients with GC/GEJ with CPS ≥1 (Cohort B1) or CPS <1 (Cohort B2). Despite the important benefit of ICI or ICI-based therapy in GC/GEJ, not all patients respond to treatment, and some move on to progression after an initial response. As ICI-based treatment moves to earlier line, it will be important to explore alternative treatment to rescue this population for whom the prognosis is poor on chemotherapy standard of care in later treatment lines. In Cohort B3, the potential to rescue patients who will have progressed on prior ICI-based treatment will be investigated.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Please refer to the master protocol for risk assessment for SAR444245, 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 when combined with pembrolizumab results from anticipated risks for SAR444245 and from the label information for Keytruda® (pembrolizumab), taking into account potential overlapping risks. The available safety data for pembrolizumab, along with proposed mitigation strategies are summarized below and also provided in Table 11.

2.3.1.1 Pembrolizumab

Pembrolizumab potentiates T-cell responses, including antitumor responses, through blockade of PD1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment (TME).

The use of pembrolizumab may cause IRRs (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, and hypersensitivity. Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated adverse events are designated as important identified risks for pembrolizumab (30).

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Among the immune-related AEs (irAEs) associated with pembrolizumab are: immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis, immune-related endocrinopathies, immune-related skin adverse reactions and other additional clinically significant, immune-related adverse reactions (reported in clinical studies or in post-marketing experience): uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, and myelitis.

Efficacy and safety data for pembrolizumab from patients ≥75 years are limited. In this population, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Please refer to the country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for pembrolizumab for more detailed information.

2.3.1.2 SAR444245 combined with pembrolizumab

Combining SAR444245 with pembrolizumab may lead to an increased frequency and/or severity of adverse events (AEs) related to immune activation or may lead to additional AEs related to immune system activation for each substance individually or may cause occurrences of qualitatively different AEs. Serious adverse drug reactions reported with agents known to increase immune activation include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction (see Section 2.3.1.1).

As both substances are biologic agents, they may have the propensity to induce infusion-related reactions that may have higher rate of occurrence and severity when SAR444245 with pembrolizumab are used in combination.

The maximum tolerated dose (MTD) of SAR444245 combined with the approved dosing of the anti PD-1 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.

2.3.2 Benefit assessment

More detailed information about the expected benefits of SAR444245 may be found in the master protocol, and the combination of SAR444245 and pembrolizumab are provided below.

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).

Immune checkpoint inhibitors are approved in most of the indications proposed to be tested in this study (please refer to Section 2.1 - Study Rationale): ESCC, gastric and gastroesophageal, HCC. In gastric cancer and ESCC, the main benefit of pembrolizumab is brought to patients with diseases that have a relatively high expression of PD-L1 (CPS ≥10). Combining SAR444245 to pembrolizumab is anticipated to expand to population responding to the an anti-PD1 and to increase the quality of the response. Such effects have been demonstrated in the PIVOT-02 study for bempegaldesleukin combined with nivolumab in metastatic melanoma, achieving deep and durable responses with rates of CR of 34% and PFS (30.9 months) exceeding that reported in clinical trials for approved treatments (31). Objective responses were also documented in PDL1 negative cases (n=13), with an ORR of 39% and 3 patients achieving 100% reduction of target lesions, and 2 patients achieving CR. Echoing these results are those of the same combination in 1L metastatic urothelial carcinoma, an indication where response to immune checkpoint is linked to the level of expression of PD-L1. In this study, bempegaldesleulin when combined with nivolumab induced significant ORR with 17% CR, with ORR similar and PD-L1 negative (50%) and PD-L1 positive (56%) (15), which contrast with data from Keynote-052 for pembrolizumab (32, 33). Combining SAR444245 with pembrolizumab is anticipated to bring benefit to patients with ESCC and GC/GEJ even in the context of low PD-L1 and could rescue patients who have progressed or relapsed following an anti-PD1/PD-L1.

2.3.3 Overall benefit: risk conclusion

More detailed information about the expected benefits of SAR444245 may be found in the master protocol.

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 pembrolizumab are justified by the anticipated benefits that may be afforded to participants with GC/GEJ.

2.3.4 Benefit and risk assessment in the context of COVID-19 pandemic

Please refer to the master protocol for more details about risks related to the patient population, SAR444245 treatment, and study related activity.

In addition, the impact of PD-1 blockade therapy on Coronavirus disease 2019 (COVID-19) severity was also explored by 2 groups and did not find a clinically meaningful signal (34, 35).

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 1 - Objectives and endpoints

Objectives	Endpoints
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Cohorts B1, B2 and *B3* will assess SAR444245 adding on to pembrolizumab in participants with advanced unresectable or metastatic gastric cancer (GC) or Siewert Type 2 & 3 gastro-esophageal junction adenocarcinoma (GEJ) and for whom receiving standard of care (SOC) is not in his or her best interest (for example, participants who are not eligible, cannot tolerate, decline to receive, or have no access to such treatment) or where no SOC is established. MSI-H cases will not be eligible. HER2 + cases will not be eligible unless they have progressed on a trastuzumab-based treatment.

- *Cohorts B1 & B2* participants must not have received more than two prior lines of treatment that did not include an anti-PD1/PD-L1-based regimen. Participants will be assigned to one of these 2 cohorts according to the level of PD-L1 expression at baseline using the CPS as follow:
  - *Cohort B1:* participants with CPS ≥1 GC/GEJ
  - *Cohort B2*: participants with CPS <1 GC/GEJ
- *Cohort B3* participants are eligible regardless of the disease CPS status and must have received at least one and no more than three prior lines of treatment and have progressed after primary or secondary resistance to an anti-PD1/PD-L1-based regimen (detailed in Section 5.1).

Please refer to the master protocol for a full description of the study design, and for details applicable to all therapy cohorts.

A graphical presentation of the substudy schema is shown in Figure 1. For treatment period, the completion of Cycle 35 is applicable for Cohorts B1, B2, and B3.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with the anti-PD1 antibody pembrolizumab will result in a significant increase in the population experiencing an objective response.
The design of the 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 RECIST 1.1 for participants with advanced unresectable and metastatic GC/GEJ.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB).
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications. And
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5- fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohorts B1, B2, and B3 specific criteria.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply (in addition to the criteria listed in the master protocol):

Type of participant and disease characteristics

I 01. Histologically or cytologically confirmed diagnosis of GC or Siewert Type 2 & 3 GEJ.

I 02. Confirmed diagnosis at study entry of advanced unresectable or metastatic disease.

PD-L1 expression using CPS as determined at local laboratory with an approved test (please refer to the lab manual for details on PD-L1 assay)

I 03. *For participants in Cohort B1*: Disease with CPS scoring of ≥1.

I 04. *For participants in Cohort B2*: Disease with CPS scoring of <1.

Note: *For participants in Cohort B3*: Disease with any CPS scoring. No need for CPS determination at local laboratory.

I 05. MSI status: Participants must have MSI status known, determined locally and must have non-MSI-H disease to be eligible.

I 06. Other genetic aberrations: Participants with unknown HER2/neu status must have their HER2/neu status determined locally. Participants with HER2/neu negative are eligible. Participants with HER2/neu positive tumors must have documentation of disease progression on treatment containing trastuzumab to be eligible.

Prior anticancer therapy

I 07. *For participants in Cohorts B1, and B2*: Participants for whom available SOC should not be in their best interest and should have failed or relapsed on no more than 2 prior lines of treatment, and which did not include an anti-PD-1/PD-L1-based treatment. See instructions specific to Korea in Appendix 7 (Section 10.7).

I 08. *For participants in Cohort B3*: Participants should have received at least one but no more than 3 prior lines of treatment, including an anti-PD-1/PDL-1 containing regimen and have progressed after a primary or secondary resistance to an anti-PD-1/PDL-1. See instructions specific to Korea in Appendix 7 (Section 10.7).

Note: For Cohorts B3:

Primary resistance is defined as a patient who has experienced progressive disease (PD) or SD lasting <6 months of initiation of PD-1/PD-L1 inhibitor-based treatment and who received at least 6 weeks of the PD1/PD-L1. Radiographic confirmation of the PD must be documented after a minimum of 4 weeks after the initial identification of progression, unless: i) investigator confirms clinical progression/ deterioration attributed to PD, or ii) the first radiographic assessment indicated critical tumor growth by imaging (size or location).

Or

Secondary resistance: patients must have experienced PD, either during or within 3 months of discontinuing treatment with anti-PD1-based therapy, occurring after previous clear benefit (any complete [CR] or partial response [PR]), or after previous stable disease (SD) >6 months. No requirement for radiographic confirmation of progression.

I 09. An anti-PD1/PD-L1 containing regimen is defined as either an anti-PD1/PD-L1 monotherapy, or an anti-PD1/PD-L1 agent administered in the same cycle as another systemic anticancer therapy. If PD1/PD-L1 was used beyond initial radiological progression while continuing to use the same PD1/PD-L1 agent used before PD, it is still considered as the same regimen. The site's study team must have reviewed previous tumor assessments (including screening tumor imaging) to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the anti-PD1/PD-L1 containing regimen.

I 10. Provision of tumor tissue:

- **Mandatory baseline biopsy** for participants in **Cohorts B1, B2, and B3,** : minimum 5 slides with 4-5 micron thickness for the first 20 participants who have signed ICF (excluding screen failure participants), minimum 10 slides with 4-5 micron thickness for subsequent participants in each cohort. Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- **Optional on-treatment biopsy** for Cohorts B1, B2, and B3 per Investigator's discretion and evaluation.
- 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.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply (in addition to the criteria listed in the master protocol):

Prior/concomitant therapy

E 01. For participants in Cohorts B1 and B2: Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD-1/PD-L1 but have written confirmation they were on control arm are allowed).

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

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

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

For study treatment duration, completion of Cycle 35 is applicable for Cohorts B1, B2, and B3.

Dosing sequence: [redacted]

In addition, if a participant has immune unconfirmed progression of disease (iUPD) and is clinically stable, it is at the discretion of the Investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed (iCPD) at least 4 weeks, but no longer than 8 weeks from the date of the scan suggesting progression of disease (Section 10.9).

6.1.1 Investigational medicinal product (IMP)

Investigation medicinal product is defined as SAR444245 and pembrolizumab administered in combination as described in Section 4. Details of each IMP component to be administered are shown in Table 2.

Preparation and administration of IMP are detailed in the pharmacy manual.
Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 2 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	100 mg/vial
Dosage level(s)[a]	24 µg/kg Q3W	200 mg Q3W
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	See master protocol	IMP
Packaging and labeling	See master protocol	Supplied in single dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.
Current/Former name(s) or alias(es)	See master protocol	Keytruda

a See master protocol.

6.1.2 Non-investigational medicinal products

Please refer to the master protocol.

In case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, SAR444245 premedication no longer needs to be administered.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications for SAR444245 are permitted according to the guidelines described in this section. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

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, Day 1 should be delayed for all IMPs) is permitted in case of treatment-emergent adverse event (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.

In participants who have SAR444245 dose reduction due to SAR444245 related Grade ≥3 treatment-related adverse events (TRAEs), SAR444245 dose may be re-escalated to[redacted] µg/kg if:

- no SAR444245 related Grade ≥3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND
- both Investigator and Sponsor agree that the participant has clinical benefit.

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 of the master protocol 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 all IMP components are permanently discontinued, it is full permanent discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.5.2 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 the next dose after recovery from the toxicity as described in Section 6.5.3 and Section 6.5.4. After cycle is delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline.

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 delay, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for the delay should be documented in the participant's study record.

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

Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 3-8) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline .

The dose of SAR444245 should be reduced to [redacted]µg/kg (with the exception of lymphocytopenia which is directly associated with SAR444245 mode-of-action and does not require dose reduction) in cases of:

- First occurrence of Grade 3 TRAE that does not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 TRAE of any duration.
- Grade 4 TRAE.
- First occurrence of Grade 3 laboratory abnormality that are clinically significant per Section 10.3.1 of the master protocol. and that do not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 clinically significant laboratory abnormality of any duration.
- Grade 4 laboratory abnormalities that are clinically significant.

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

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

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.

Recommended guidelines for the management of specific adverse events including irAE, CRS, Vascular Leak Syndrome (VLS) and Infusion-related reactions (IRR) are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as adverse events of special interest (AESIs), depending on grading according to National Cancer Institute- Common Terminology Criteria for Adverse Event (NCI-CTCAE) V5.0 (see Section 8.3.8 of the master protocol). In case a specific adverse event meets the AESI definition it must be documented in the e-CRF.

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol 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.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 3.

After an infusion-related reaction due to pembrolizumab infusion (Grade 3 or Grade 4), the SAR444245 infusion will be delayed and can be administered after resolution of symptoms. The Investigator should discuss with the Sponsor's Medical Monitor if the SAR444245 infusion needs to be delayed more than 1 day.

Guidelines for the management of SAR444245 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, please see Section 6.1.2.1 of the master protocol.

Table 3 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - Epinephrine*, - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics, - Oxygen, - Pressors, - Corticosteroids. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Table 4 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE 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 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	SAR444245 infusion should be interrupted if applicable. If symptoms resolve within 1 hour of interrupting 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 should be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. The next infusion should be given 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 (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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.
Grade 4 Life-threatening; pressor or ventilator support indicated	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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 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: nonsteroidal anti-inflammatory drugs.

6.5.4.2 Anaphylaxis

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

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) (37, 38, 39).

6.5.4.3 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 V5.0 and managed according to institutional standards.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (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 C-reactive protein (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 according to severity grading are provided in Table 5. ASTCT CRS consensus grading scale is provided in Section 10.11 of the master protocol.

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

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] 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 participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during 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. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants 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. SAR444245 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 SAR444245 dose modification and supportive care guidelines
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	<u>If CRS grade 3, SAR444245 should be temporarily delayed, and subsequent treatment should be resumed only when symptoms have resolved or improved to Grade 1.</u> SAR444245 can be either restarted at [redacted]µg/kg or permanently discontinued, as clinically indicated. <u>If CRS Grade 4, SAR444245 should be permanently discontinued, as clinically indicated.</u> If CRS Grade 3 or Grade 4, IV corticosteroids should be initiated (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, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants 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 should be discussed with clinical site specialists

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b 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.

c 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.

d 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: 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; IL = Interleukin; IMP=investigational medicinal product; IV = Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.5.4.4 Immune-related adverse events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. IrAEs are thought to be caused by unrestrained cellular immune responses directed at the normal host tissues. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing pembrolizumab clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care.

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 severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 6. Of note, when study interventions are administered in combination, 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.

The CTCAE V5.0 must be used to grade the severity of AEs.

When pembrolizumab can be restarted, it should be administered at the initial planned dose and schedule as no modification is allowed:

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.

  If the toxicities do resolve and conditions are aligned with what is defined in Table 6, the combination of SAR444245 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 6 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab and SAR444245 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab and SAR444245 have been withheld pembrolizumab and SAR444245 may be resumed after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold[a]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue[b]		
Diarrhea/Colitis	Grade 2 or 3	Withhold[a]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis 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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		
AST or ALT elevation or Increased Bilirubin	Grade 2[c]	Withhold[a]	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper. Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
	Grade 3[d] or 4[e]	Permanently discontinue[b]		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a f]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2 Grade 3 or 4	Withhold[a] Withhold[a] or permanently discontinue[b f]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
Hyperthyroidism	Grade 2 Grade 3 or 4	Continue Withhold[a] or permanently discontinue[b f]	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Neurological Toxicities	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
All Other irAEs	Persistent Grade 2	Withhold[a]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold[a] or discontinue based on the event[g]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up

a SAR444245 to be withheld plus pembrolizumab to be withheld corresponds to "cycle delay".
b Permanently discontinuation of full study treatment.
c AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal.
d AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal.
e AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.
f The decision to withhold or permanently discontinue pembrolizumab and SAR444245 is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab and SAR444245 may be resumed.
g Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).
AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

6.5.4.5 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 10.11 of the master protocol). Recommendations for ICANS management mainly include the use of 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 SAR444245 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.	SAR444245 [a] should be delayed. Treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to ■ µg/kg 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	If Grade 3 ICANS, SAR444245 should be delayed. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at ■ µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor.

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
EEG that resolve with intervention. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 4 ICANS, SAR444245 should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 5 in Section 6.5.4.3. 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, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants 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 clinical specialists should be involved whenever indicated.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual
Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; ICANS= Immune effector cell associated neurotoxicity syndrome; ICE= Immune Effector Cell-Associated Encephalopathy; IV = Intravenous.

6.5.4.6 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 (1).

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

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Moderate Grade 2 Symptomatic; medical intervention indicated	SAR444245 should be delayed. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. 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	If Grade 3 or Grade 4 VLS, SAR444245 should be permanently discontinued. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids.
Grade 4: Life-threatening consequences; urgent intervention indicated	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 Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AKI= acute kidney injury; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; MW= molecular weight; NCI = National Cancer Institute; VLS= vascular leak syndrome.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for definition and treatment of SAR444245 overdose.

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol and Section 1.3.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

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

Please refer to the master protocol for RECIST 1.1.

[redacted]

8.2 SAFETY ASSESSMENTS

Please refer to the master protocol.

In addition, combining SAR444245 with other anticancer therapies may increase the frequency and severity of immune-related adverse events related to other anticancer therapies. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level will be monitored.

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

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information.

Please refer to the master protocol for AEs and serious adverse events (SAEs) collection. For participants in Cohort B1, B2 and B3 irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

For pembrolizumab, SAEs that are considered expected will be specified in the reference safety information (country-approved product labeling for pembrolizumab).

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Please refer to the master protocol.

In addition, symptomatic or asymptomatic overdose with pembrolizumab are described as below:

- An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

8.10 PATIENT-REPORTED OUTCOMES (PRO)

[redacted]

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

The plan is to treat approximately 40 participants per cohort for Cohorts B1, B2, and B3.

Table 9 lists estimated ORR and 90% exact confidence intervals (CIs) by number of responders from a sample size of 40 participants treated.

Table 9 - Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
2	5% (0.9% - 14.9%)
4	10% (3.5% - 21.4%)
6	15% (6.7% - 27.5%)
8	20% (10.4% - 33.2%)
10	25% (14.2% - 38.7%)
12	30% (18.3% - 44.0%)
14	35% (22.6% - 49.2%)

CI: confidence interval; N=number.

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 these cohorts.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

In addition, efficacy analyses will be performed by pooled cohorts B1 and B2.

9.4.2 Primary endpoint(s)

Please refer to the master protocol.

9.4.3 Secondary endpoint(s)

Please refer to the master protocol.

9.4.4 Tertiary/exploratory endpoint(s)

[redacted].

9.4.4.1 Exploratory antitumor indicators

[redacted].

9.4.4.2 Patient-reported outcomes

[redacted]

9.4.5 Other safety analysis

Please refer to the master protocol.

9.4.6 Other analysis

Please refer to the master protocol.

9.5 INTERIM ANALYSES

Please refer to the master protocol.

For each cohort, if the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 15% for cohort B1, 5% for cohort B2, 10% for cohort B3) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

Please refer to the master protocol.

10.1.2 Financial disclosure

Please refer to the master protocol.

10.1.3 Informed consent process

Please refer to the master protocol.

10.1.4 Data protection

Please refer to the master protocol.

10.1.5 Committees structure

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

Please refer to the master protocol.

10.1.7 Data quality assurance

Please refer to the master protocol.

10.1.8 Source documents

Please refer to the master protocol.

10.1.9 Study and site start and closure

Please refer to the master protocol.

10.1.10 Publication policy

Please refer to the master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohorts B1, B2, and B3 specific evaluations are presented in Table 10.

Table 10 - Protocol-required laboratory tests

Laboratory tests	Parameters
Endocrine function tests[a]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

NOTES :

a Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT in cohorts receiving pembrolizumab. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

South Korea:

Korean participants with gastric cancer or gastro-esophageal junction adenocarcinoma will not be enrolled in Cohort B1 or Cohort B2 to receive SAR444245 in combination with pembrolizumab as 1st or 2nd line (L) treatment neither in Cohort B3 to receive SAR444245 + pembrolizumab as 2nd L.

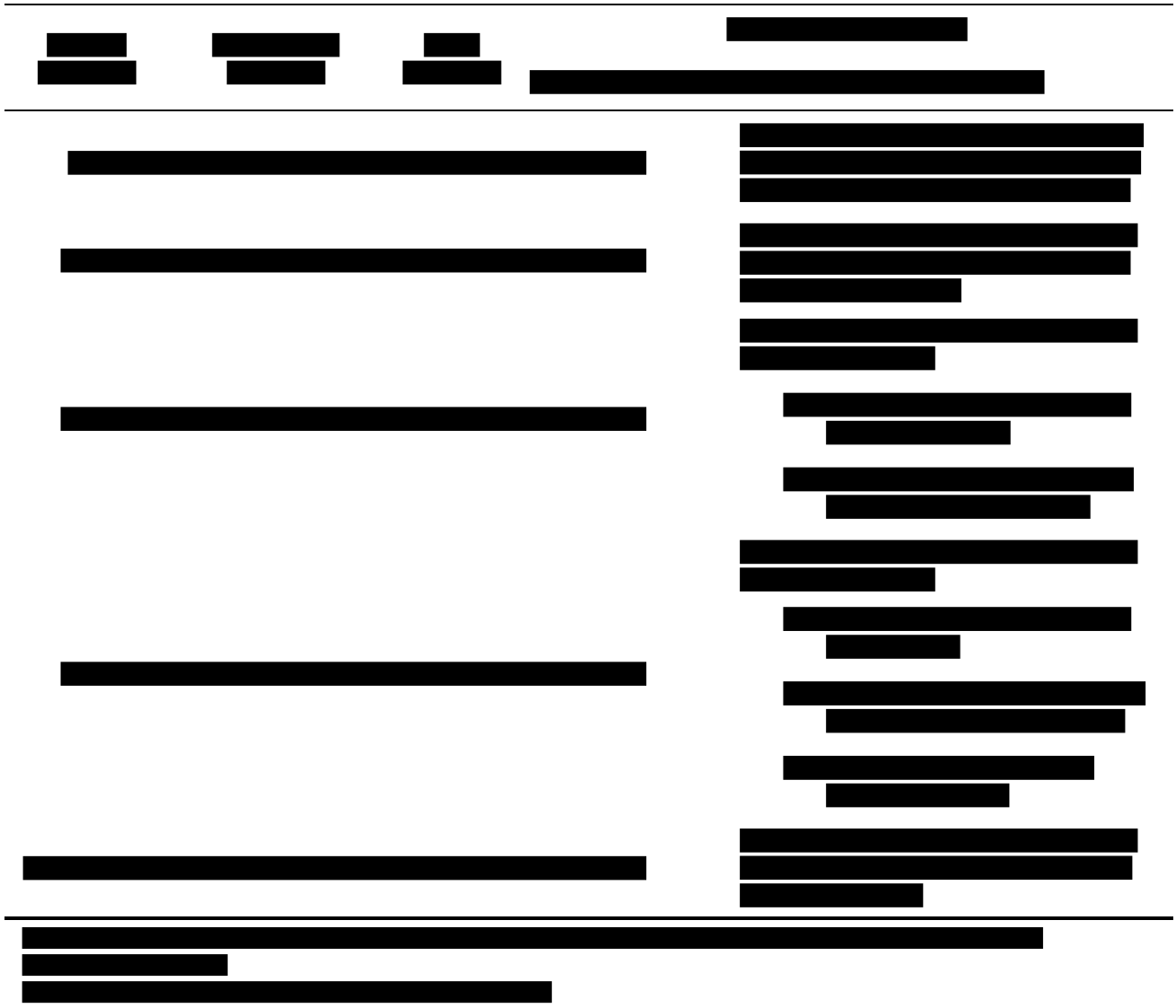
Please refer to the master protocol for additional country specific requirements.

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

Please refer to the master protocol.

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 or[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. 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: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Please refer to the master protocol.

10.11 APPENDIX 11: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245, available information about pembrolizumab is shown in Table 11.

Table 11 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion-related reactions are provided in Table 3.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.
Hepatotoxicity	Pembrolizumab Hepatitis occurred in 0.8% of patients, including Grade 2, 3 or 4 cases in 0.1%, 0.5% and 0.1% patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.6 months (range 8 days to 21.4 months). The median duration was 1.1 months (range 1 day to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 0.3% patients. Hepatitis resolved in 36 patients.	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
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 6.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 6.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 6.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly.
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.8 of the master protocol.

10.12 APPENDIX 12: ASTCT ASSESSMENT FOR ICANS AND CRS

Please refer to the master protocol.

10.13 APPENDIX 13: ABBREVIATIONS

AESIs: adverse events of special interest
ASTCT: American Society for Transplantation and Cellular Therapy
CR: complete response
[redacted]
e-CRF: electronic case report form
EOT: end of treatment
GC: gastric cancer
GEJ: gastro-esophageal junction adenocarcinoma
ICANS: immune cell-associated neurotoxicity syndrome
ICU: intensive care unit
[redacted]

IRR: infusion-related reactions
NCI-CTCAE: National Cancer Institute- Common Terminology Criteria for Adverse Event
NHP: non-human primate
[redacted]
PD1: programmed cell death protein 1
[redacted]
PK: pharmacokinetic
PRO: patient reported outcome
SAEs: serious adverse events
TEAE: treatment-emergent adverse event
TIL: tumor infiltrating lymphocytes
VLS: vascular leak syndrome

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

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

10.14.1 Amended protocol 01 (30 August 2021)

This amended protocol (Amendment 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 overall rationale for the amendment is to include stopping rules for futility, update the rules for dose modification in case of treatment-related adverse events (TRAEs), and clarify the population for Cohorts B1, B2 and B3 in substudy 02.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 4.1 Study design	The following sentence has been added "for example, participants who are not eligible, cannot tolerate, decline to receive, or have no access to such treatment" to clarify the population for Cohort B1, B2, and B3.	For clarity.
Section 1.1 Synopsis	In Figure 1, the following sentences have been added as footnote "* In 1L, when receiving standard of care (SOC) is not in the best interest of the participant	For consistency.

Section # and Name	Description of Change	Brief Rationale
	** non-MSI-H and HER2 negative (or HER2 positive if progression is noted on trastuzumab based therapy)".	
Section 5.1 Inclusion Criteria	In I06, "- less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "-less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment".	Harmonization per program level approach.
Section 6.5.1 General rules	The following sentence has been deleted "Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.", and the following sentences have been added "In participants who have SAR444245 dose reduction due to SAR444245 related Grade ⩾3 TRAEs, SAR444245 dose may be re-escalated to [redacted] µg/kg if: •no SAR444245 related Grade ⩾3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND •both Investigator and Sponsor agree that the participant has clinical benefit.".	For clarification of how dose will be reduced and re-escalated for participants who experience any Grade ⩾3 TRAEs.
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following sentence "Participants who experience Grade ⩾3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) will be required to temporarily delay the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy." has been changed to "Participants who experience Grade ⩾3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 3-8) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline". Dose reduction rules have added, and the following sentence has been deleted "Dose reduction for SAR444245 from [redacted] µg/kg to [redacted] µg/kg (or another lower recommended dose) may be decided when specified in the protocol or following discussions with the Sponsor." .	For consistency and clarity.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 4 under Grade 3 and Grade 4, "prematurely" has been removed from "prematurely permanently discontinued".	For clarity.
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 5 under Grade 3, the following sentence was deleted "If subsequent administration is tolerated, increasing the SAR444245 dose to ■ µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor".	For consistency.
Section 9.5 Interim analyses	The following sentences have been added "For each cohort, if the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 15% for cohort B1, 5% for cohort B2, 10% for cohort B3) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.".	To include stopping rules for futility.

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40. [redacted]

41. [redacted]

Signature Page for VV-CLIN-0617849 v3.0
act16902-16-1-1-amended-protocol02-substudy02

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 02 (SUBSTUDY 03)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants with advanced and metastatic hepatocellular carcinoma**
Protocol number:	**ACT16902-S03**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab for the treatment of participants with hepatocellular carcinoma**
Study phase:	**Phase 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):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02 (Substudy 03)	All	12 January 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 03)	All	30 August 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 03)		20 July 2021, version 1 (electronic 1.0)

Amended protocol 02 (12 January 2022)

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 main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Belgian, Italian, German (Federal Institute for Drugs and Medical Devices [BfArM]), and South Korean Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA is provided for this substudy with procedures taken from the master protocol. And the previous footnote a for endocrine function tests has been renumbered as footnote j in the current document.	Regulatory Authorities (BfArM) request.
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up Visit 1.	To allow assessment of any potential cardiotoxity.
1.4 Biomarker flowchart	A complete Table of biomarker flowchart is provided for this substudy with biomarker sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.
1.5 Pharmacokinetic flowcharts	Complete Tables of pharmacokinetic (PK) flowcharts are provided for this substudy with PK sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.

Section # and Name	Description of Change	Brief Rationale
8.1.1 Assessment of objective response using the most appropriate modality according to the nature of the measurable lesion(s)	The following sentence has been removed "To account for the possibility of unconventional immune responses, participants may continue treatment beyond progression if pseudo-progression is ruled out."	For consistency.
10.9 [redacted]	[redacted].	For correction.
Throughout	Minor editorial updates.	For consistency and clarification.

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Cohort-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants with advanced and metastatic hepatocellular carcinoma

Brief title: A study of SAR444245 combined with pembrolizumab for the treatment of participants with hepatocellular carcinoma

Rationale:

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 CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of complete responses (CR) and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with an anti-PD1 antibody.

PD1/PD-L1-based regimens have been approved as 1L or 2L therapy for advanced unresectable or metastatic hepatocellular carcinoma (HCC). Rescue of patients who will have failed ICI-containing regimens is crucial for later line therapies. This proposed study aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with the anti-PD1 antibody pembrolizumab will result in a significant increase in the percentage of patients experiencing an objective response in participants with advanced unresectable or metastatic HCC who relapsed on prior PD1/PD-L1-based regimens.

Objectives and endpoints

Please refer to the master protocol.

Overall design:

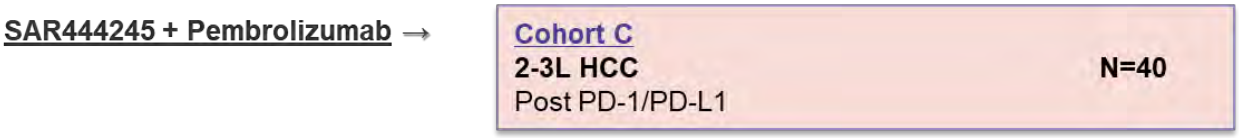
Please refer to the master protocol.

Brief summary:

Cohort C will assess SAR444245 adding on to pembrolizumab in participants with advanced unresectable or metastatic HCC who relapsed on prior PD1/PD-L1-based regimens, with at least SD as best response and with no more than 2 prior lines of treatment.

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

Figure 1 - Overall study schema - Substudy 03



Abbreviations: 2-3L: second-line or third-line; HCC: hepatocellular carcinoma; N=number; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in Cohort C.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration for a participant in Cohort C. For treatment period, the completion of Cycle 35 is applicable for Cohort C.

Study intervention(s)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab

- **Formulation**: Keytruda® (pembrolizumab) as 100 mg/4 mL (25 mg/mL) solution in single-dose vials
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle for **up to 35 cycles**.

Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

SAR444245

SAR444245 formulation, route of administration, and dose regimen as described in the master protocol. Treatment duration for Cohort C is up to 35 cycles.

Noninvestigational medicinal products

Please refer to the master protocol.

After 4 cycles, in case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, premedication no longer needs to be administered.

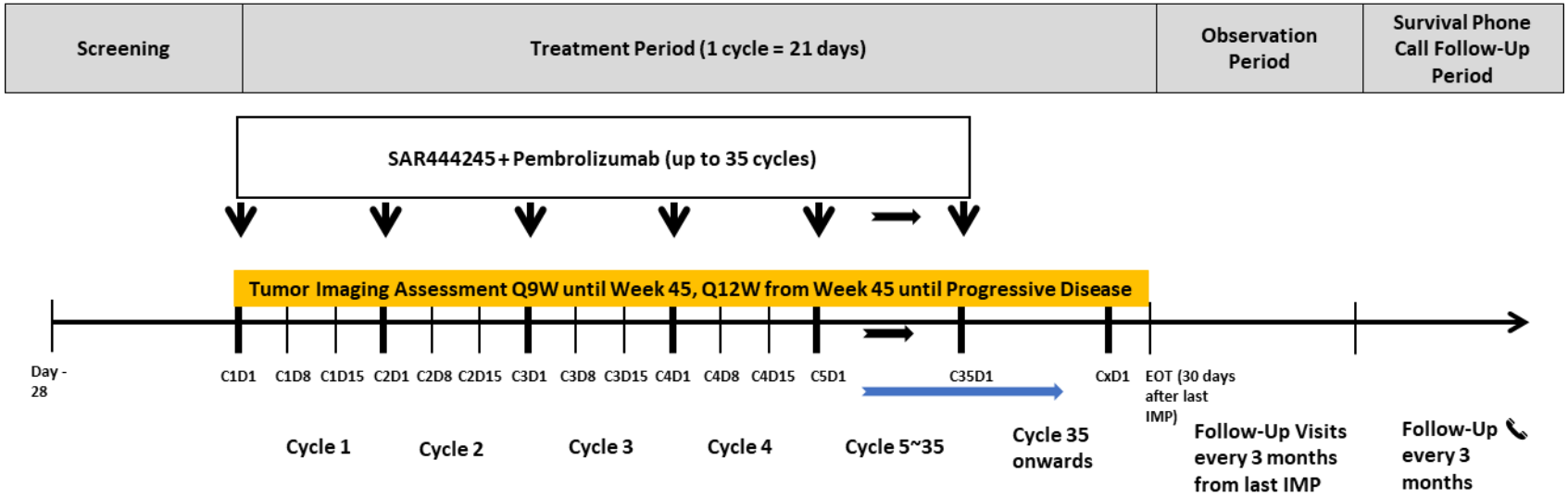
Statistical considerations:

Please refer to master protocol.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 2 - Graphical study design - Cohort C



C=Study cycle; D=Study day; EOT=end of treatment; IMP=Investigational medicinal product; Q9W=every 9 weeks; Q12W=every 12 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months+/- 14 days**	
Informed consent	X										
Inclusion and exclusion criteria	X										
IRT contact	X	X			X	X					
Demography, medical/surgical and disease history	X										See Section 8 of the master protocol
Body Weight/Height[g]	X	X	X	X	X	X	X				
Full physical examination	X					X					See Section 8.2.1 of the master protocol
Directed Physical examination		X	X	X	X		X				See Section 8.2.1 of the master protocol
Vital Signs	X	X	X	X	X	X	X				See Section 8.2.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months+/- 14 days**	
Performance status (ECOG)	X	X	X	X	X	X	X				
SpO_2	X	As clinically indicated									
Laboratory and other investigations											
12-Lead ECG	X	X	As clinically indicated								See Section 8.2.3 of the master protocol
LVEF	X	As clinically indicated									See Section 8.2.3 of the master protocol
Troponin	X	As clinically indicated			X (Cycle 4 Day 1)	As clinically indicated					See Section 8.2.3 of the master protocol and Section 10.2 of the master protocol
Pregnancy test	X	X			X	X	X	X			See Section 8.2.5 of the master protocol and Section 10.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months+/- 14 days**	
Hepatitis serology, CD4 counts and viral load	X[h]	As clinically indicated									See Section 10.2 of the master protocol and Section 10.7 of the master protocol
Hematology	X	X	X	X	X	X	X				See Section 10.2 of the master protocol
Coagulation	X	As clinically indicated									See Section 10.2 of the master protocol
Blood Chemistry	X	X	X	X	X	X	X				See Section 10.2 of the master protocol
Urinalysis[i]	X	X			X	X	X				See Section 10.2 of the master protocol
T3, FT4, TSH & cortisol[j]	X				X	X	X				See Section 10.2
AFP	X										
IMP											
SAR444245		X			X						

Evaluation[a]	Screening	Treatment Period[b]				End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]	EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**30 days (+/- 7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months+/- 14 days**	
Pembrolizumab		X			X						
Hospitalization[k]		X									
AE/SAE assessment[l]	X	Continuously throughout treatment period					X				See Sectio 8.3 of the master protocol
Prior/Concomitant Meds	X	Continuously throughout treatment period									See Section 6.8 of the master protocol
First subsequent anti-cancer therapy						X	X	X	X	X	
Survival status										X	
Pharmacokinetic (PK) / Pharmacodynamic (PDy) / Immunogenicity assessments											
PK SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
ADA SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2										
PDy - Blood and tumor tissue collection[m,n]	See Biomarker flowchart in Section 1.4										
Tumor assessment											
Brain imaging[o]	X										See Section 8.1 of the master protocol
CT/MRI[p]	X				X	X	X	X	X		See Section 8.1 of the master protocol

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. 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 first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator prior to IMP administration at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: a treatment cycle is 21 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

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 tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and 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 study.

e For Cycle 4 visits, please refer to PK flowchart in Section 1.5.

f C1D8 and/or C1D15 visits must be performed on site for the following participants only: 1) Participants scheduled to have blood draws for biomarker assessment and/or ADA on Day 8; 2) Participants who will receive IMP on Day 8 and Day 15. For all other participants, these 2 on-site visits may be done remotely as appropriate based on investigator's discretion per institutional standard and local regulations. If this is the case, this must be documented in the source document. Sponsor may decide to cancel safety assessment on C1D8 and C1D15 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 For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.7 of the master protocol).

i Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during Treatment Period and as clinically indicated.

j Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated

k Only for participants who will participate in the intensive PK sample collection.

l AE/SAE assessment: 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 (1).

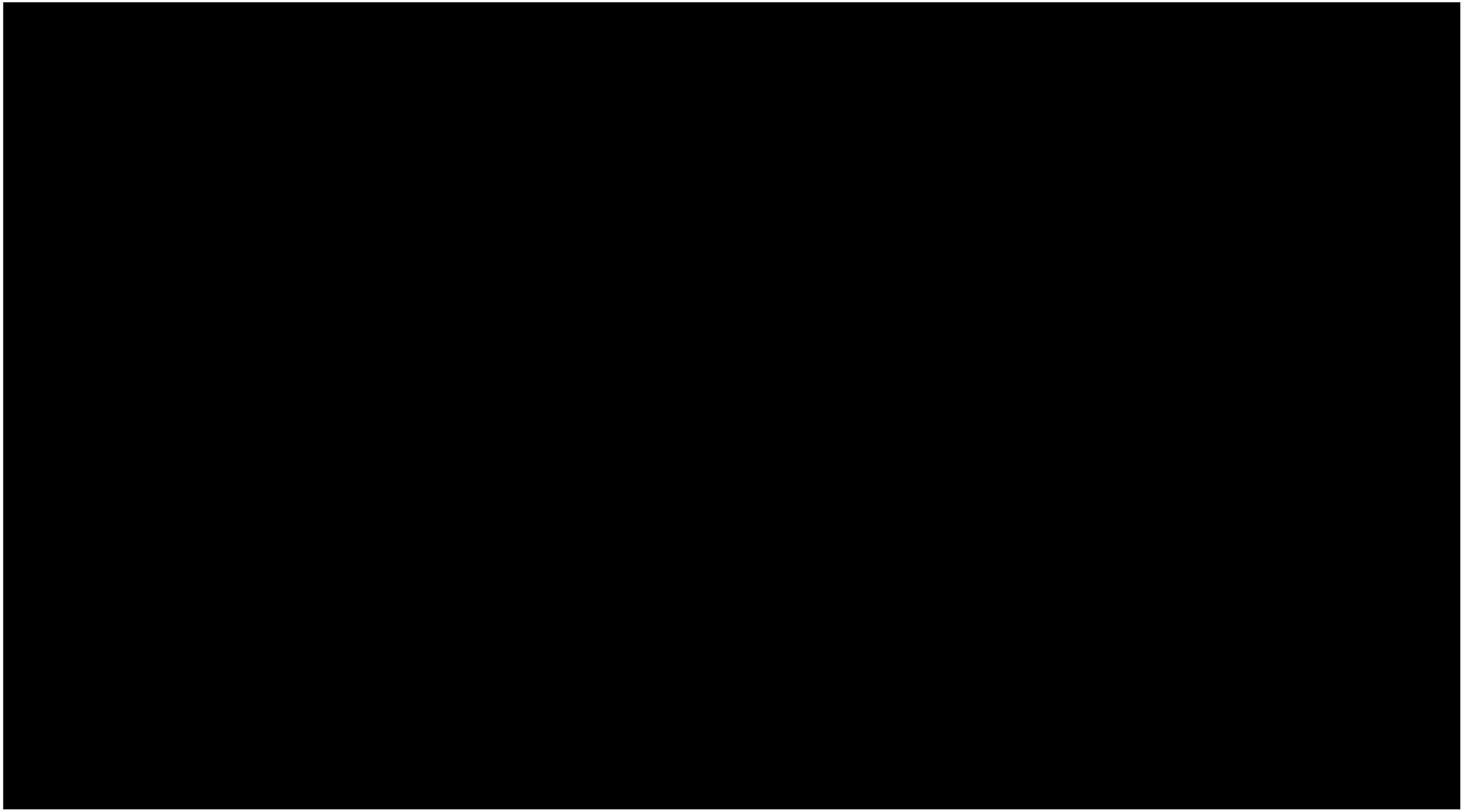
m If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

n Will not be done for participants enrolled in China.

o 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 as per protocol tumor assessment (TA) schedule. 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 4 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 have 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.

p CT/MRI: The initial tumor imaging will be performed within 28 days prior to C1D1. 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 of first IMP and 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, during treatment period until PD. Per the primary tumor assessment criteria, after the first documentation of response 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.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; AFP: alpha fetoprotein; AST=aspartate transaminase; ALT=alanine transaminase; C=Cycle; ANC=Absolute neutrophil count; AP=Alkaline phosphatase; BUN=Blood urea nitrogen; CRF=case report form; CRS=Cytokine release syndrome; CT=computed tomography; [redacted]; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FT4=free thyroxine; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; ICF=Informed consent form; IMP=investigational medicinal product; INR=international normalized ratio; LDH=Lactate hydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA= multigated acquisition; PD=progressive disease; [redacted] PDy=pharmacodynamic; PK=pharmacokinetic; PR=partial response; PS=Performance Status; SpO2= oxygen saturation; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; T3=tri-iodothyronine; TSH=thyroid stimulating hormone; WBC=White blood cells.



1.5 PHARMACOKINETIC FLOWCHARTS

For participants who will undergo more intensive pharmacokinetic (PK) sampling, the schedule is shown in the flowchart in Section 1.5.1. Up to 30 participants enrolled across cohorts treated with SAR444245 + pembrolizumab (including Cohort C) will undergo more intensive PK sampling, up to 10 participants from China will undergo intensive PK sampling.

For all other participants, the PK sampling schedule is shown in the flowchart in Section 1.5.2.

1.5.1 Participants with more intensive PK sampling

Cycle	Cycle 1										Cycle 2, 3		Cycle 4									Cycles 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	D1									D8	D1		D1									D1		
Time after SAR444245 dosing (EOI,except SOI) [h]	SOI	EOI	1	2	4	8	24	48	72	168	SOI	EOI	SOI	EOI	1	2	4	8	24	48	72	SOI	EOI	
SAR444245 PK sample ID	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08		P00[a]	P01[b]	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08	P00[a]	P01[b]	
Sample time window			±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h						±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h			
SAR444245 ADA sample ID[c]	AB00[a]									AB01	AB00[a]		AB00[a]									AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI),
b PK sample must be taken at EOI after flush.
c ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.
In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at EOI +1 h, +2 h, +4 h, +8 h, +24 h, +48 h and +72 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end of resumed infusion and subsequent samples should be drawn at 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after end of resumed infusion (as per protocol).
ADA: anti-drug antibodies; EOI: End of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: Start of infusion.

1.5.2 All other participants

Cycle	Cycle 1				Cycles 2, 3. 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit
Day	D1			D8	D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	24	168	SOI	EOI	30 (±7) days after last IMP admin
SAR444245 PK sample		P01[b]	P06[c]			P01[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI)
b EOI samples = end of infusion samples. Must be taken at end of infusion precisely
c PK sample can be collected at any time during the second day of the cycle.

ADA: anti-drug antibodies, PK: pharmacokinetic: SOI: start of infusion; EOI: end of infusion

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to cohort with advanced unresectable or metastatic HCC for the combination therapy with pembrolizumab.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models while anti-PD1 antibody prevents T cell suppression through the PD1/PD-L1 pathway. The combination of anti-PD1 treatment with SAR444245 was tested in a syngeneic mouse CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of CR and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the country approved labeling for detailed background information on pembrolizumab.

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD1 has been resolved (7). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (6, 8, 9, 10). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (13, 14, 15, 16, 17, 18, 19). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (7, 16, 18, 19, 20). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (18). Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab IB).

A summary of clinical trial data and the justification of the choice of pembrolizumab dose is provided in Section 4.3.2.

2.2.2 Rationale for HCC and selected population (Cohort C)

Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers. Worldwide, liver cancers are the 4th most common cause of cancer-related death and rank 6th in terms of incident cases (21). In Asia the global burden of HCC is declining, it is still increasing in the US and Europe (22). Liver cancer is the second most lethal tumor. More than half of patients present with advanced-stage tumor and ultimately receive palliative therapies.

Up to recently, sorafenib has been the mainstay of 1L HCC treatment. Several tyrosine kinase inhibitors (TKIs) have become available in the last few years. Lenvatinib was approved as 1L treatment for HCC in 2018 by demonstrating non-inferiority to sorafenib. In the 2L setting, regorafenib has become the first drug approved by the FDA for second-line treatment because it decreased the death risk by 37% as compared to the placebo (23). Cabozantinib and ramucirumab also received FDA approval as second-line treatment because of promising efficacy and manageable safety profile based on two RCTs (CELESTIAL and REACH-2) (24, 25). In this setting, the TKI are the current treatment options but inducing limited response rates (~4 -7%).

Otherwise, HCC is characterized by immune tolerance, with a complex array of immune cells populating the tumor microenvironment that are inactivated by local immune-suppressive signals (26), it is why Immunotherapy has become a promising therapeutic approach for HCC. The FDA has granted accelerated approval for nivolumab and pembrolizumab monotherapy for patients with HCC who have been previously been treated with sorafenib based on two studies (CheckMate-040 and KEYNOTE-224) (27, 1). Although ICI monotherapy had achieved clinically meaningful ORRs, these ORRs are still modest (15-18%) and did not translate into survival benefit. In the Phase 3 trial of KEYNOTE-240, despite an ORR of 18.3% as achieved for pembrolizumab vs. 4.4% for placebo, pembrolizumab versus placebo failed to demonstrate significant improvements in overall survival (OS) or overall survival (PFS) as these primary endpoints did not reach statistical significance per prespecified criteria (28). Furthermore, nivolumab monotherapy failed to achieve a significant primary endpoint (OS) as the 1L treatment of HCC (CheckMate 459).

Efforts have intensified to develop strategies to enhance the immune response and overall efficacy of ICIs, including combination regimens with agents that target pathways involved in tumor progression and process immunomodulatory properties (29) and these led to further investigations of combinations of immunotherapy with other modalities to increase durable responses and survival. Nivolumab combined with ipilimumab (Phase 1/2 CheckMate-040) received accelerated approval because of promising ORR (32%) and durable responses (at least 24 months over 30% of responders) in the early Phase 1/2 CheckMate-040 (30).

More recently, FDA approved atezolizumab in combination with bevacizumab as the new SoC in 1L based on the data from Phase-3 RCT (IMbrave150) where a significant improvement in both OS and PFS was observed in the atezolizumab-bevacizumab arm compared to the sorafenib arm (OS: NE versus 13.2 months; PFS: 6.8 versus 4.3 months) (29).

In summary, TKIs are main treatment options in this population, inducing very limited ORR (~5%). ICI-based regimen (atezolizumab + bevacizumab) has become the new SoC in 1L, therefore, most patients will have received an ICI before later line therapies. Rescue of patients who will have failed ICI-containing regimen in 1L will be evaluated to establish PoC of SAR444245 when combined with pembrolizumab in 2L+ HCC.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Please refer to the master protocol for risk assessment for SAR444245, 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 when combined with pembrolizumab results from anticipated risks for SAR444245 and from the label information for Keytruda® (pembrolizumab), taking into account potential overlapping risks. The available safety data for pembrolizumab, along with proposed mitigation strategies are summarized below and also provided in Table 13.

2.3.1.1 Pembrolizumab

Pembrolizumab potentiates T-cell responses, including antitumor responses, through blockade of PD1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment (TME).

The use of pembrolizumab may cause IRRs (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, and hypersensitivity). Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated adverse events are designated as important identified risks for pembrolizumab (31).

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Among the immune-related AEs (irAEs) associated with pembrolizumab are: immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis, immune-related endocrinopathies, immune-related skin adverse reactions and other additional clinically significant, immune-related adverse reactions (reported in clinical studies or in post-marketing experience): uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, and myelitis.

Efficacy and safety data for pembrolizumab from patients ≥75 years are limited. In this population, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Please refer to the country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for pembrolizumab for more detailed information.

2.3.1.2 SAR444245 combined with pembrolizumab

Combining SAR444245 with pembrolizumab may lead to an increased frequency and/or severity of adverse events (AEs) related to immune activation or may lead to additional AEs related to immune system activation for each substance individually or may cause occurrences of qualitatively different AEs. Serious adverse drug reactions reported with agents known to increase immune activation include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction (see Section 2.3.1.1).

As both substances are biologic agents, they may have the propensity to induce infusion-related reactions that may have higher rate of occurrence and severity when SAR444245 with pembrolizumab are used in combination.

The maximum tolerated dose (MTD) of SAR444245 combined with the approved dosing of the anti PD-1 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.

2.3.2 Benefit assessment

More detailed information about the expected benefits of SAR444245 may be found in the master protocol, and the combination of SAR444245 and pembrolizumab are provided below.

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).

2.3.3 Overall benefit: risk conclusion

More detailed information about the expected benefits of SAR444245 may be found in the master protocol.

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 pembrolizumab are justified by the anticipated benefits that may be afforded to participants with HCC.

2.3.4 Benefit and risk assessment in the context of COVID-19 pandemic

Please refer to the master protocol for more details about risks related to the patient population, SAR444245 treatment, and study related activity.

In addition, the impact of PD-1 blockade therapy on Coronavirus disease 2019 (COVID-19) severity was also explored by 2 groups and did not find a clinically meaningful signal (32, 33).

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 1 - Objectives and endpoints

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Cohort C will assess SAR444245 adding on to pembrolizumab in participants with advanced unresectable or metastatic hepatocellular carcinoma (HCC) who relapsed on prior PD1/PD-L1-based regimens, with at least SD as best response and with no more than 2 prior lines of treatment.

Please refer to the master protocol for a full description of the study design, and for details applicable to all therapy cohorts.

A graphical presentation of the substudy schema is shown in Figure 1. For treatment period, the completion of Cycle 35 is applicable for Cohort C.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with the anti-PD1 antibody pembrolizumab will result in a significant increase in the population experiencing an objective response.

The design of the 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 RECIST 1.1 for participants with advanced and metastatic HCC.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB).
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications. And
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5- fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort C specific criteria.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply (in addition to the criteria listed in the master protocol):

Type of participant and disease characteristics

I 01. Histologically or cytologically confirmed diagnosis of HCC, or clinically by AASLD criteria in cirrhotic patients (patients without cirrhosis must have had histological confirmation of diagnosis).

I 02. Confirmed diagnosis at study entry of advanced unresectable or metastatic disease.

Note: *For participants in Cohort C*: Disease with any CPS scoring. No need for CPS determination at local laboratory.

I 03. Prior anticancer therapy: Participants must have received 1 or 2 prior lines of treatment per local standard of care, including an anti-PD-1/PDL-1 treatment, have progressed on or after an anti-PD-1/PD-L1 treatment and have had at least stable disease (SD) as best response on this anti-PD-1/PD-L1-based treatment.

I 04. Provision of tumor tissue:

- **Optional baseline biopsy** per Investigator's discretion and evaluation of participants in **Cohort C**.
- **Optional on-treatment biopsy** for Cohort C per Investigator's discretion and evaluation.
- 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.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply (in addition to the criteria listed in the master protocol):

Medical conditions

E 01. Participants with Child-Pugh class B or C.

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

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

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

For study treatment duration, completion of Cycle 35 is applicable for Cohort C.

Dosing sequence: [redacted]

6.1.1 Investigational medicinal product (IMP)

Investigation medicinal product is defined as SAR444245 and pembrolizumab administered in combination as described in Section 4. Details of each IMP component to be administered are shown in Table 2.

Preparation and administration of IMP are detailed in the pharmacy manual.

Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 2 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	100 mg/vial
Dosage level(s)[a]	24 µg/kg Q3W	200 mg Q3W
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	See master protocol	IMP
Packaging and labeling	See master protocol	Supplied in single dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.
Current/Former name(s) or alias(es)	See master protocol	Keytruda

a See master protocol.

6.1.2 Non-investigational medicinal products

Please refer to the master protocol.

In case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, SAR444245 premedication no longer needs to be administered.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications for SAR444245 are permitted according to the guidelines described in this section. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

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, Day 1 should be delayed for all IMPs) is permitted in case of treatment-emergent adverse event (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.

In participants who have SAR444245 dose reduction due to SAR444245 related Grade ≥3 treatment-related adverse events (TRAEs), SAR444245 dose may be re-escalated to[redacted] µg/kg if:

- no SAR444245 related Grade ≥3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND
- both Investigator and Sponsor agree that the participant has clinical benefit.

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 of the master protocol 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 all IMP components are permanently discontinued, it is full permanent discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.5.2 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 the next dose after recovery from the toxicity as described in Section 6.5.3 and Section 6.5.4. After cycle is delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline.

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 delay, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for the delay should be documented in the participant's study record.

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

Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 3-8) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline.

The dose of SAR444245 should be reduced to [redacted] µg/kg (with the exception of lymphocytopenia which is directly associated with SAR444245 mode-of-action and does not require dose reduction) in cases of:

- First occurrence of Grade 3 TRAE that does not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 TRAE of any duration.
- Grade 4 TRAE.
- First occurrence of Grade 3 laboratory abnormality that are clinically significant per Section 10.3.1 of the master protocol. and that do not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 clinically significant laboratory abnormality of any duration.
- Grade 4 laboratory abnormalities that are clinically significant.

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

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

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.

Recommended guidelines for the management of specific adverse events including irAE, CRS, Vascular Leak Syndrome (VLS) and Infusion-related reactions (IRR) are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as adverse events of special interest (AESIs), depending on grading according to National Cancer Institute- Common Terminology Criteria for Adverse Event (NCI-CTCAE) V5.0 (see Section 8.3.8 of the master protocol). In case a specific adverse event meets the AESI definition it must be documented in the e-CRF.

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol 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.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 3.

After an infusion-related reaction due to pembrolizumab infusion (Grade 3 or Grade 4), the SAR444245 infusion will be delayed and can be administered after resolution of symptoms. The Investigator should discuss with the Sponsor's Medical Monitor if the SAR444245 infusion needs to be delayed more than 1 day.

Guidelines for the management of SAR444245 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, please see Section 6.1.2.1 of the master protocol.

Table 3 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - Epinephrine*, - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics, - Oxygen, - Pressors, - Corticosteroids. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Table 4 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE 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 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	SAR444245 infusion should be interrupted if applicable. If symptoms resolve within 1 hour of interrupting 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 should be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. The next infusion should be given 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 (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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.
Grade 4 Life-threatening; pressor or ventilator support indicated	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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 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: nonsteroidal anti-inflammatory drugs.

6.5.4.2 Anaphylaxis

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

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) (35, 36, 37).

6.5.4.3 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 V5.0 and managed according to institutional standards.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (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 C-reactive protein (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 according to severity grading are provided in Table 5. ASTCT CRS consensus grading scale is provided in Section 10.11 of the master protocol.

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

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] 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 participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during 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. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants 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. SAR444245 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 SAR444245 dose modification and supportive care guidelines
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 3, SAR444245 should be temporarily cycle delayed, and subsequent treatment should be resumed only when symptoms have resolved or improved to Grade 1 at ■ µg/kg or permanently discontinued, as clinically indicated. If CRS Grade 4, SAR444245 should be permanently discontinued, as clinically indicated. If CRS Grade 3 or Grade 4, IV corticosteroids should be initiated (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, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants 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 should be discussed with clinical site specialists

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b 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.

c 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.

d 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: 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; IL = Interleukin; IMP=investigational medicinal product; IV = Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.5.4.4 Immune-related adverse events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. IrAEs are thought to be caused by unrestrained cellular immune responses directed at the normal host tissues. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing pembrolizumab clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab and/or SAR444245, administration of corticosteroids and/or other supportive care.

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 severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 6. Of note, when study interventions are administered in combination, 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.

The CTCAE V5.0 must be used to grade the severity of AEs.

When pembrolizumab can be restarted, it should be administered at the initial planned dose and schedule as no modification is allowed:

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 6, the combination of SAR444245 or pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 6 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab and SAR444245 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab and SAR444245 have been withheld, pembrolizumab and SAR444245 may be resumed after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold[a]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue[b]		
Diarrhea/Colitis	Grade 2 or 3	Withhold[a]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis 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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		
AST or ALT elevation or Increased Bilirubin/hepatitis	Grade 2[c]	Withhold[a]	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
	Grade 3[d] or 4[e]	Permanently discontinue[b]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a, f]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2 Grade 3 or 4	Withhold[a] Withhold[a] or permanently discontinue[b, f]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
Hyperthyroidism	Grade 2 Grade 3 or 4	Continue Withhold[a] or permanently discontinue[b, f]	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Neurological Toxicities	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
All Other irAEs	Persistent Grade 2	Withhold[a]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold[a] or discontinue based on the event[g]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		

a SAR444245 to be withheld plus pembrolizumab to be withheld corresponds to "cycle delay".
b Permanently discontinuation of full study treatment.
c AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal.
d AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal.
e AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.
f The decision to withhold or permanently discontinue pembrolizumab and SAR444245 is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab and SAR444245 may be resumed.
g Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).
AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

6.5.4.5 Immune cell-associated neurotoxicity syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) 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 10.11 of the master protocol). Recommendations for ICANS management mainly include the use of 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 SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Moderate Grade 2 ICE score 3-6. Awakens to voice.	SAR444245 [a] should be delayed. Treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to ■ µg/kg 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. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 3 ICANS, SAR444245 should be delayed. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at ■ µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. If Grade 4 ICANS, SAR444245 should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 5 in Section 6.5.4.3. 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, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants 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 clinical specialists should be involved whenever indicated.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual
Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; ICANS= Immune effector cell associated neurotoxicity syndrome; ICE= Immune Effector Cell-Associated Encephalopathy; IV = Intravenous.

6.5.4.6 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 (1).

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

Event severity (NCI-CTCAE V5.0)	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	SAR444245 should be delayed. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] kg. 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. In participants 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 Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AKI= acute kidney injury; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; MW= molecular weight; NCI = National Cancer Institute; VLS= vascular leak syndrome.

6.5.4.7 Hepatic Events

Hepatic events (HEs) as described in Section 8.3.8. All these HEs will require holding study intervention with an immediate assessment:

All participants should be considered for evaluation according to the directions below within 72 hours of the alert for AESI.

- Procedures:
  - Consider obtaining a consultation with a hepatologist

- Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
- Assess for ingestion of drugs/supplements with hepatotoxic potential
- Assess for alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, INR, and complete blood count with differential
- Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
- HBV DNA, HBsAg, HBeAg, anti-HBc (total and IgM), anti-HBe, and anti-HBs regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in approximately 1-2% of participants who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC participants in this study. The recommendation is to hold study interventions (cycle delay when SAR444245 is withhold + pembrolizumab is withhold). If toxicity does not improve within 1 to 2 days or worsens, follow “Management of HE for Pembrolizumab/SAR4444245” below.

Table 9 - Management of HE associated with Pembrolizumab and SAR444245

	Diagnosis	Management
Hepatitis B consider flare or change in HBV immunologic status	Rapid elevation of ALT to >5 × ULN and/or >3 × baseline	Interrupt pembrolizumab and SAR444245 interventions for up to 12 weeks. Start antiviral therapy or check for compliance if HBV is detectable. Measure safety labs for AST, ALT, ALP, T Bili, D Bili, and INR on weekly basis. Measure HBsAg and HBV DNA on weekly basis (if detected at the time of onset of ECI). Evaluate the following every 2-3 weeks: anti-HBe, HBe antigen, anti-HBs, and HBV DNA levels (if not detected at the onset of ECI) Restart pembrolizumab and SAR444245 intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should have permanent full discontinuation of study interventions

	Diagnosis	Management
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to >5 × ULN and/or >3x baseline	Interrupt pembrolizumab and SAR444245 interventions for up to 12 weeks. Assess use of injection or inhalation drugs.
Relapse of HCV infection for participants with successfully treated or new HCV infection	If HCV RNA was TND at baseline, and now has confirmed detectable HCV RNA (2 specimens, 1 week apart)	Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection. Measure safety labs for AST, ALT, ALP, T Bili, D Bili, and INR on weekly basis Measure HCV RNA levels every 2 weeks. Please discuss risk benefit with Sponsor prior to starting HCV antiviral therapy. Restart pembrolizumab and SAR444245 interventions only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should have a permanent full discontinuation of study interventions.
Immune-related Hepatitis	If any of the HECI criteria is met as defined in the protocol Section 8.3.8 Note: Immune-related hepatitis is a diagnosis made after excluding other possible etiologies such as viral flare, biliary or vascular obstruction, infection, medications, and alcohol use usually immune-related hepatitis response to dechallenge and/or steroids and re-occurs with rechallenge	Interrupt pembrolizumab and SAR444245 interventions for up to 12 weeks. Start IV corticosteroid 60 mg/day of prednisone or equivalent followed by oral corticosteroid. Monitor with biweekly laboratory tests, including AST, ALT, T Bili, D Bili, ALP, and INR. Restart pembrolizumab and SAR444245 intervention only if: Abnormal laboratory values resolve to Grade ≤1 or baseline (if abnormal at baseline) Taper steroid over 28 days Steroid treatment is tapered to prednisone <10 mg/day or equivalent Permanently fully Discontinue pembrolizumab and SAR444245 intervention if: Laboratory abnormalities do not resolve within 3 weeks Steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks Decompensation to CP-C status
Other Causes	Rule out infection with blood, urine, and ascites culture - antibiotics should be started if infection is found If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging Ruled out alcohol use and hepatotoxic drugs including herbal and alternative medications	Restart pembrolizumab and SAR444245 only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.

Abbreviations: ALT= alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; D Bili=direct bilirubin, HBe= hepatitis B e antigen; HBs= hepatitis B surface antigen; HBV= hepatitis B virus; HCV= hepatitis C virus; HECI= Hepatic Events of Clinical Interest; INR= international normalized ratio, IV=intravenous; T Bili=total bilirubin, TND= target not detected.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for definition and treatment of SAR444245 overdose.

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol and Section 1.3.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

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

Please refer to the master protocol for RECIST 1.1.

[redacted]

[redacted]

8.2 SAFETY ASSESSMENTS

Please refer to the master protocol.

In addition, combining SAR444245 with other anticancer therapies may increase the frequency and severity of immune-related adverse events related to other anticancer therapies. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level will be monitored.

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

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information.

Please refer to the master protocol for AEs and serious adverse events (SAEs) collection. For participants in Cohort C irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

For pembrolizumab, SAEs that are considered expected will be specified in the reference safety information (country-approved product labeling for pembrolizumab).

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Please refer to the master protocol.

Hepatic Events (HEs) include any of the following events if the events are considered not due to disease progression as judged by the investigator

- ALT:
  - **a)** Among subjects with Baseline ALT <2 × ULN: ALT ≥5 × ULN
  - **b)** Among subjects with Baseline ALT ≥2 × ULN: ALT >3 × the Baseline level
  - **c)** ALT >500 U/L regardless of baseline level
- Total Bilirubin:
  - **a)** Total bilirubin >3.0 mg/dL
- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  - New onset clinically detectable ascites requiring intervention for >3 days

- Hepatic Encephalopathy

In addition, symptomatic or asymptomatic overdose with pembrolizumab are described as below:

- An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

For participants to Cohort C (HCC), tumor biopsy is optional.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

The plan is to treat approximately 40 participants in Cohort C.

Table 10 lists estimated ORR and 90% exact confidence intervals (CIs) by number of responders from a sample size of 40 participants treated.

Table 10 - Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
2	5% (0.9% - 14.9%)
4	10% (3.5% - 21.4%)
6	15% (6.7% - 27.5%)
8	20% (10.4% - 33.2%)
10	25% (14.2% - 38.7%)
12	30% (18.3% - 44.0%)
14	35% (22.6% - 49.2%)

CI: confidence interval; N=number.

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 cohort.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

Please refer to the master protocol.

9.4.3 Secondary endpoint(s)

Please refer to the master protocol.

9.4.4 Tertiary/exploratory endpoint(s)

[redacted].

9.4.4.1 Exploratory antitumor indicators

[redacted]

9.4.5 Other safety analysis

Please refer to the master protocol.

9.4.6 Other analysis

Please refer to the master protocol.

9.5 INTERIM ANALYSES

Please refer to the master protocol.

If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5%) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

Please refer to the master protocol.

10.1.2 Financial disclosure

Please refer to the master protocol.

10.1.3 Informed consent process

Please refer to the master protocol.

10.1.4 Data protection

Please refer to the master protocol.

10.1.5 Committees structure

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

Please refer to the master protocol.

10.1.7 Data quality assurance

Please refer to the master protocol.

10.1.8 Source documents

Please refer to the master protocol.

10.1.9 Study and site start and closure

Please refer to the master protocol.

10.1.10 Publication policy

Please refer to the master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort C specific evaluations are presented in Table 11.

Table 11 - Protocol-required laboratory tests

Laboratory tests	Parameters
Endocrine function tests[a]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

NOTES :

a Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT in cohorts receiving pembrolizumab. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

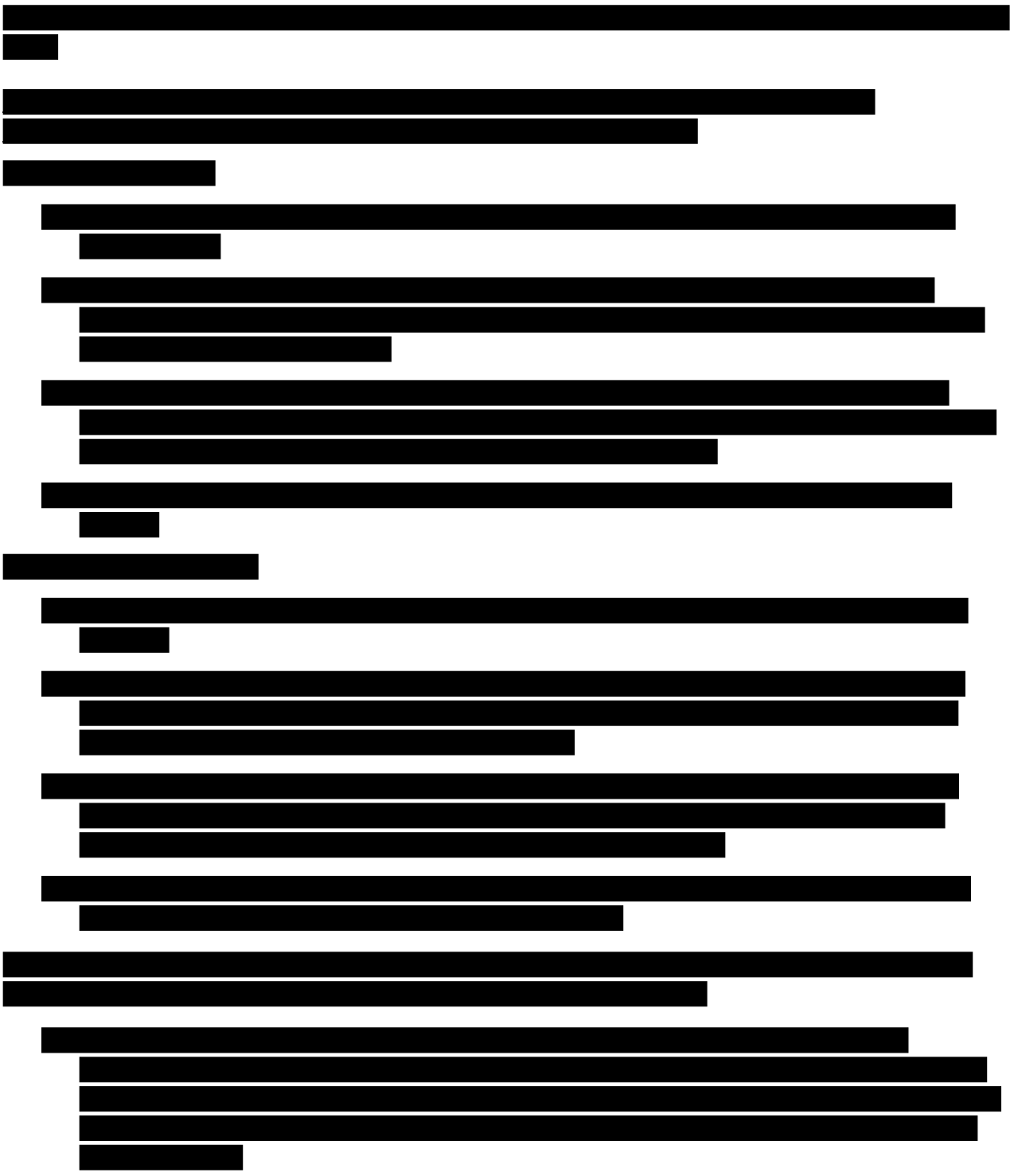
10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol.

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

Please refer to the master protocol.

10.9 APPENDIX 9: [redacted]



[redacted]

10.10 APPENDIX 10: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Please refer to the master protocol.

10.11 APPENDIX 11: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245, available information about pembrolizumab is shown in Table 13.

Table 13 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion associated reactions are provided in Table 4.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.
Hepatotoxicity	Pembrolizumab Hepatitis occurred in 0.8% of patients, including Grade 2, 3 or 4 cases in 0.1%, 0.5% and 0.1% patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.6 months (range 8 days to 21.4 months). The median duration was 1.1 months (range 1 day to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 0.3% patients. Hepatitis resolved in 36 patients.	Dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Table 6.
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 6.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 6.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 6.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly.
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.8 of the master protocol.

10.12 APPENDIX 12: ASTCT ASSESSMENT FOR ICANS AND CRS

Please refer to the master protocol.

10.13 APPENDIX 13: ABBREVIATIONS

AESIs: adverse events of special interest
ASTCT: American Society for Transplantation and Cellular Therapy
CR: complete response
[redacted]
e-CRF: electronic case report form
EOT: end of treatment
HCC: hepatocellular carcinoma
ICANS: immune cell-associated neurotoxicity syndrome
ICU: intensive care unit
[redacted]
IRR: infusion-related reactions
NCI-CTCAE: National Cancer Institute- Common Terminology Criteria for Adverse Event
NHP: non-human primate
[redacted]
PD1: programmed cell death protein 1
[redacted]
PK: pharmacokinetic
SAEs: serious adverse events
TEAE: treatment-emergent adverse event
TIL: tumor infiltrating lymphocytes
VLS: vascular leak syndrome

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

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

10.14.1 Amended protocol 01 (30 August 2021)

This amended protocol (Amendment 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 overall rationale for the amendment is include stopping rules for futility and update the rules for dose modification in case of treatment-related adverse events (TRAEs) for Cohort C in substudy 03.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 2.3.2 Benefit assessment	The following sentences have been deleted "Non-MSI-H mCRC are known to not respond to immune checkpoint inhibitors, being qualified as immune excluded or restricted tumors. Combining SAR444245 may unleash inflammatory response in the tumor microenvironment and sensitize CRC to anti-PD1."	Correction for consistency.
Section 5.1 Inclusion Criteria	In I06, "- less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "-less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment".	Harmonization per program level approach
Section 6.5.1 General rules	The following sentence has been deleted "Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.", and the following sentences have been added "In participants who have SAR444245 dose reduction due to SAR444245 related Grade ≥3 TRAEs, SAR444245 dose may be re-escalated to[redacted] µg/kg if: no SAR444245 related Grade ≥3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND both Investigator and Sponsor agree that the participant has clinical benefit.".	For clarification of how dose will be reduced and re-escalated for participants who experience any Grade ≥3 TRAEs.
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following sentence "Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) will be required to temporarily delay the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy." has been changed to "Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 3-8) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline". Dose reduction rules have added, and the following sentence has been deleted "Dose reduction for SAR444245 from [redacted] µg/kg to [redacted] µg/kg (or another lower recommended dose) may be decided when specified in the protocol or following discussions with the Sponsor."	For consistency and clarity.
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 4 under Grade 3 and Grade 4, "prematurely" has been removed from "prematurely permanently discontinued".	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 5 under Grade 3, the following sentence was deleted "If subsequent administration is tolerated, increasing the SAR444245 dose to ■ µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor".	For consistency.
Section 9.5 Interim analyses	The following sentences have been added "If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5%) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.".	To include stopping rules for futility.

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act16902-16-1-1-amended-protocol02-substudy03

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 02 (SUBSTUDY 04)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab or cetuximab for the treatment of participants with advanced and metastatic colorectal cancer**
Protocol number:	**ACT16902-S04**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab or cetuximab for the treatment of participants with colorectal cancer**
Study phase:	**Phase 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:	156424
EudraCT:	2021-002181-41
NCT:	NCT05104567
WHO:	U1111-1251-4981

Date: 12-Jan-2022 Total number of pages: 82

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02 (Substudy 04)	All	12 January 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 04)	All	30 August 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 04)		20 July 2021, version 1 (electronic 1.0)

Amended protocol 02 (12 January 2022)

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 main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Belgian, Italian, German (Federal Institute for Drugs and Medical Devices [BfArM]), and South Korean Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA is provided for this substudy with procedures taken from the master protocol. And the previous footnote a for endocrine function tests has been renumbered as footnote j in the current document.	Regulatory Authorities (BfArM) request.
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up Visit 1.	To allow assessment of any potential cardiotoxity.
1.4 Biomarker flowchart	A complete Table of biomarker flowchart is provided for this substudy with biomarker sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.
1.5 Pharmacokinetic flowcharts	A complete Table of pharmacokinetic (PK) flowcharts is provided for this substudy with PK sample collections taken from the master protocol.	Regulatory Authorities (BfArM) request.

Section # and Name	Description of Change	Brief Rationale
6.5.4.1 Infusion-related reactions (IRR)	In Table 7, pembrolizumab was removed for Grade 3 or 4.	For consistency since Table 7 describes cetuximab infusion-related reaction dose modification and treatment guidelines.
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	The following sentence has been added "Cetuximab may be associated with CRS. CRS typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion of cetuximab. Cetuximab related IRR's, including CRS, are discussed in Section 6.5.4.1. Please refer to Table 7 for Cetuximab IRR dose modifications and treatment guidelines."	To include information on cytokine-release syndrome reported with cetuximab and providing recommended guidelines for management.
	Table 8 has been updated with Recommended Cetuximab dose modifications and supportive care guidelines.	

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Cohort-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab or cetuximab for the treatment of participants with advanced and metastatic colorectal cancer

Brief title: A study of SAR444245 combined with pembrolizumab or cetuximab for the treatment of participants with colorectal cancer

Rationale:

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 CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of complete responses (CR) and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with an anti-PD1 antibody.

Clinical data from the on-going monotherapy dose escalation of SAR444245 (HAMMER study) has indicated a peripheral increase in the number of NK cells. NK cells are important effector cells which mediate antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab. In vitro data where NK cells pretreated with SAR444245 and then co-cultured with the EGFR-expressing A431 cancer cells improved the ADCC function of cetuximab in a dose-dependent fashion. These data support the evaluation of SAR444245 in combination with cetuximab.

The proposed study aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with either the anti-PD1 antibody pembrolizumab or with the anti-EGFR IgG1 antibody cetuximab will result in a significant increase in the percentage of patients experiencing an objective response in the setting of advanced unresectable or metastatic colorectal cancer (mCRC).

Objectives and endpoints

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 1 - Objectives and endpoints

Objectives	Endpoints
Secondary	
• To assess active concentrations of cetuximab when given in combination with SAR444245	• C_{trough} and $C_{end\ of\ infusion}$ of cetuximab

Overall design:

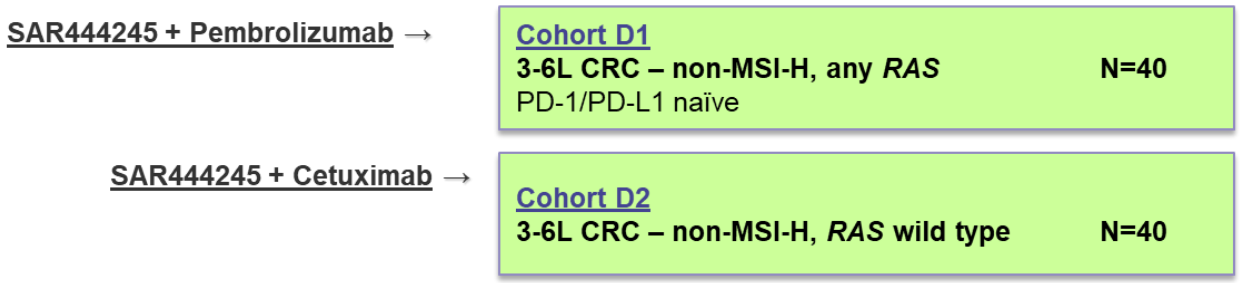
Please refer to the master protocol.

Brief summary:

Cohorts D1 and *D2* will assess SAR444245 adding on to either pembrolizumab or cetuximab, respectively, in participants with advanced unresectable or mCRC who have progressed on prior regimens having contained fluoropyrimidine, oxaliplatin, irinotecan, with either bevacizumab or cetuximab, and with no more than 5 prior lines of treatments. Patients are not eligible if MSI-H. Patients with *RASmut* are not eligible for enrollment in Cohort D2.

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

Figure 1 - Overall study schema - Substudy 04



Abbreviations: 3-6L: third-line to sixth-line; CRC: colorectal carcinoma; MSI-H: high-level microsatellite instability; N=number; PD-1: programmed cell death 1; PD-L1: programmed cell death- ligand 1.

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in each cohort for Cohorts D1 and D2.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration for a participant in Cohorts D1 and D2. For treatment period, the completion of Cycle 35 is only applicable for Cohort D1.

Study intervention(s)

Cohort D1 (SAR444245 + pembrolizumab)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab

- **Formulation**: Keytruda® (pembrolizumab) as 100 mg/4 mL (25 mg/mL) solution in single-dose vials
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle for **up to 35 cycles**.

Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

SAR444245

SAR444245 formulation, route of administration, and dose regimen as described in the master protocol. Treatment duration for Cohort D1 is up to 35 cycles.

Noninvestigational medicinal products

Please refer to the master protocol.

After 4 cycles, in case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, premedication no longer needs to be administered.

Cohort D2 (SAR444245 + cetuximab)

Dosing sequence: [redacted]

Investigational medicinal products

[redacted].

Cetuximab

Cetuximab will be administered [redacted].

- Formulation:
  - a clear, colorless solution for injection provided as 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL in a single-dose vial

    or
  - 100 mg/20 mL or 500 mg/100 mL

    or
  - any other cetuximab formulation approved locally.
- Route of administration: IV infusion

Dose regimen: Cetuximab will be given on Cycle 1 Day 1 as an initial loading dose of 400 mg/m^2 infused over 120 minutes (maximum infusion rate 10 mg/min, or as per local practice and labels) followed by 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) for all subsequent doses starting with the Cycle 1 Day 8 administration, **until PD**.

Noninvestigational medicinal products

Premedication for SAR444245 as described in the master protocol.

Premedication for cetuximab

All participants who will receive cetuximab should be premedicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions (IRs).

Each dose of cetuximab will be followed by a 1-2 hours observation period. If there are no reported infusion-related reactions (IRRs) during this observation period, then the SAR444245 dose may be administered at applicable dosing visits.

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

Statistical considerations:

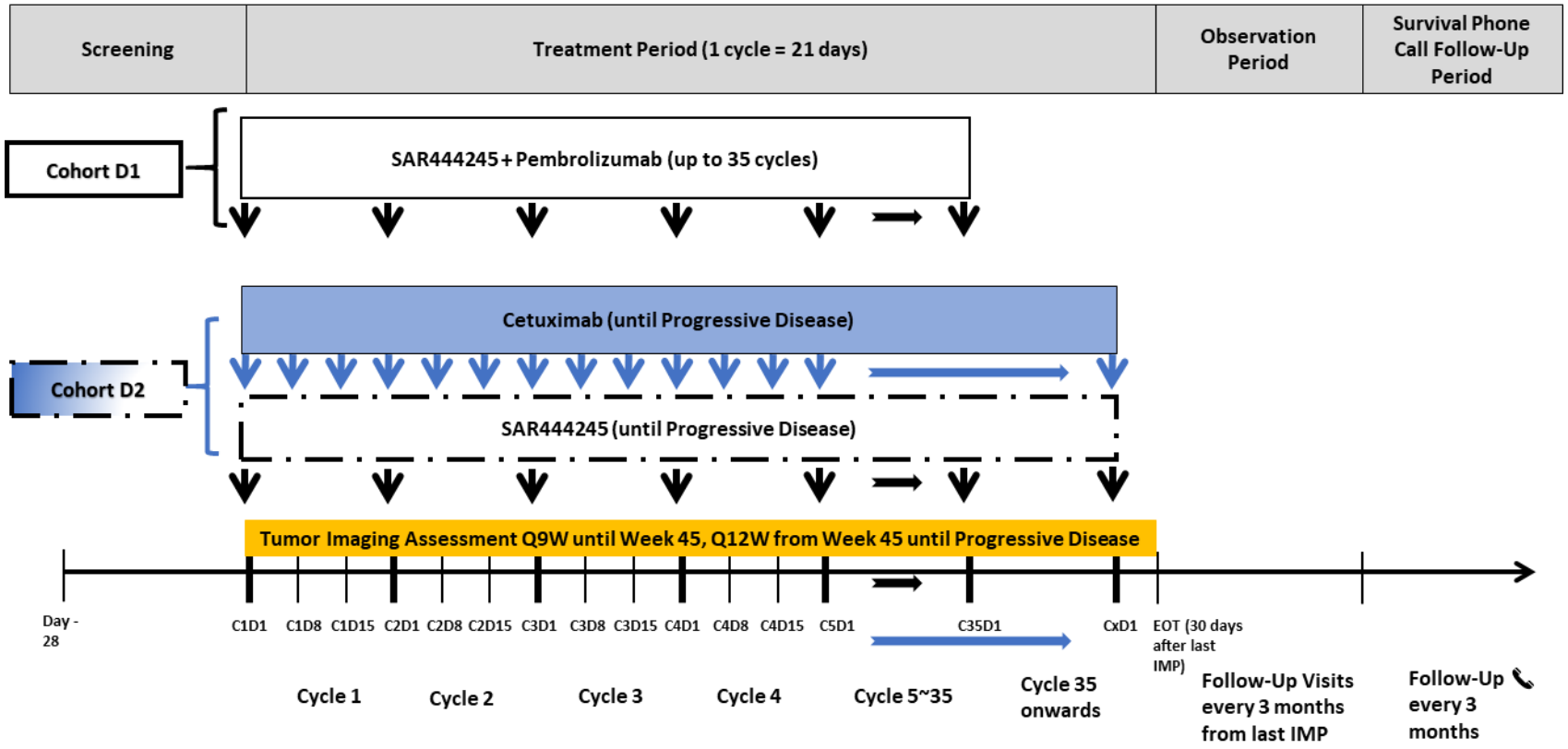
Please refer to the master protocol for description of common statistical considerations. Substudy-specific analyses are summarized below.

- Active concentrations of cetuximab when given in combination with SAR444245 will be analyzed with descriptive statistics.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 2 - Graphical study design - Cohort D1 and D2



C=Study cycle; D=Study day; EOT=end of treatment; IMP=Investigational medicinal product; Q9W= every 9 weeks; Q12W=every 12 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]						End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]			EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 days (+/-7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months +/-14 days**	
Informed consent	X												
Inclusion and exclusion criteria	X												
IRT contact	X	X			X			X					
Demography, medical/surgical and disease history	X												See Section 8 of the master protocol
Body Weight/ Height[g]	X	X	X	X	X			X	X				
Full physical examination	X							X					See Section 8.2.1 of the master protocol
Directed Physical examination		X	X	X	X				X				See Section 8.2.1 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]						End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]			EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 days (+/-7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months +/-14 days**	
Vital Signs	X	X	X	X	X			X	X				See Section 8.2.2 of the master protocol
Performance status (ECOG)	X	X	X	X	X			X	X				
SpO_2	X	As clinically indicated											
Laboratory and other investigations													
12-Lead ECG	X	X	As clinically indicated										See Section 8.2.3 of the master protocol
LVEF	X	As clinically indicated											See Section 8.2.3 of the master protocol
Troponin	X	As clinically indicated			X (Cycle 4 Day 1)			As clinically indicated					See Section 8.2.3 of the master protocol and Section 10.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]						End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]			EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 days (+/-7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months +/-14 days**	
Pregnancy test	X	X			X			X	X	X			See Section 8.2.5 of the master protocol and Section 10.2 of the master protocol
Hepatitis serology, CD4 counts and viral load	X[h]	As clinically indicated											See Section 10.2 of the master protocol and Section 10.7 of the master protocol
Hematology	X	X	X	X	X			X	X				See Section 10.2 of the master protocol
Coagulation	X	As clinically indicated											See Section 10.2 of the master protocol
Blood Chemistry	X	X	X	X	X			X	X				See Section 10.2 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]						End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]			EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 days (+/-7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months +/-14 days**	
Urinalysis[i]	X	X			X			X	X				See Section 10.2 of the master protocol
T3, FT4, TSH & cortisol (Cohort D1 only)[j]	X				X			X	X				See Section 10.2
Electrolytes (Cohort D2 only)		weekly under treatment and then at the end of treatment, at FU Visit 1 and as clinically indicated											
IMP													
SAR444245		X			X								
Pembrolizumab (Cohort D1 only)		X			X								
Cetuximab (Cohort D2 only)		X	X	X	X	X	X						
Hospitalization[k]		X											
AE/SAE assessment[l]	X	Continuously throughout treatment period							X				See Section 8.3 of the master protocol
Prior/Concomitant Meds	X	Continuously throughout treatment period											See Section 6.8 of the master protocol

Evaluation[a]	Screening	Treatment Period[b]						End of Treatment	Observation Period[c]			Survival Phone Call Follow-up[d]	Notes
		Cycle 1			Cycle 2 and beyond[e]			EOT Visit	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3+	Phone Call FU	
Cycle Day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8[f] (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 days (+/-7 days) after last IMP or at initiation of further therapy**	**3 months after last IMP admin ±7 days**	**6 months after last IMP admin ±7 days**	**Every 3 months after FU Visit 2 ±7 days**	**Every 3 months +/-14 days**	
First subsequent anti-cancer therapy								X	X	X	X	X	
Survival status												X	
Pharmacokinetic (PK) / Pharmacodynamic (PDy) / Immunogenicity assessments													
PK SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2												
PK Cetuximab	See PK flowcharts in Section 1.5												
ADA SAR444245	See PK flowcharts in Section 1.5.1 and Section 1.5.2												
PDy - Blood and tumor tissue collection[m,n]	See Biomarker flowchart in Section 1.4												
Tumor assessment													
Brain imaging[o]	X												See Section 8.1 of the master protocol
CT/MRI[p]	X				X			X	X	X	X		See Section 8.1 of the master protocol

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. 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 first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator prior to IMP administration at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: a treatment cycle is 21 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

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 tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and 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 study.

e For Cycle 4 visits, please refer to PK flowchart in Section 1.5.

f C1D8 and/or C1D15 visits must be performed on site for the following participants only: 1) Participants scheduled to have blood draws for biomarker assessment and/or ADA on Day 8; 2) Participants who will receive IMP on Day 8 and Day 15. For all other participants, these 2 on-site visits may be done remotely as appropriate based on investigator's discretion per institutional standard and local regulations. If this is the case, this must be documented in the source document. Sponsor may decide to cancel safety assessment on C1D8 and C1D15 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 For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.7 of the master protocol).

i Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal), will be performed every 4 cycles during Treatment Period and as clinically indicated.

j Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated

k Only for participants who will participate in the intensive PK sample collection.

l AE/SAE assessment: 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 (1).

m If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

n Will not be done for participants enrolled in China.

o 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 as per protocol tumor assessment (TA) schedule. 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 4 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 have 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.

p CT/MRI: The initial tumor imaging will be performed within 28 days prior to C1D1. 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 of first IMP and 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, during treatment period until PD. Per the primary tumor assessment criteria, after the first documentation of response 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.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; AST=aspartate transaminase; ALT=alanine transaminase; C=Cycle; ANC=Absolute neutrophil count; AP=Alkaline phosphatase; BUN=Blood urea nitrogen; CRF=case report form; CRS=Cytokine release syndrome; CT=computed tomography; [redacted]; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FT4=free thyroxine; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; ICF=Informed consent form; IMP=investigational medicinal product; INR=international normalized ratio; LDH=Lactate hydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA= multigated acquisition; PD=progressive disease; [redacted]; PDy=pharmacodynamic; PK=pharmacokinetic; PR=partial response; PS=Performance Status; SpO2= oxygen saturation; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; T3=tri-iodothyronine; TSH=thyroid stimulating hormone; WBC=White blood cells.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHARTS

For participants who will undergo more intensive pharmacokinetic (PK) sampling, the schedule is shown in the flowchart in Section 1.5.1. Up to 30 participants enrolled across cohorts treated with SAR444245 + pembrolizumab (including Cohort D1) will undergo more intensive PK sampling, up to 10 participants from China will undergo intensive PK sampling.

For all other participants, the PK sampling schedule is shown in the flowchart in Section 1.5.2.

1.5.1 Participants with more intensive PK sampling

Cycle	Cycle 1										Cycle 2, 3		Cycle 4									Cycles 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	D1									D8	D1		D1									D1		
Time after SAR444245 dosing (EOI, except SOI) [h]	SOI	EOI	1	2	4	8	24	48	72	168	SOI	EOI	SOI	EOI	1	2	4	8	24	48	72	SOI	EOI	
SAR444245 PK sample ID	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08		P00[a]	P01[b]	P00[a]	P01[b]	P02	P03	P04	P05	P06	P07	P08	P00[a]	P01[b]	
Sample time window			±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h						±15 min	±30 min	±30 min	±30 min	±4 h	±6 h	±8 h			
SAR444245 ADA sample ID[c]	AB00[a]									AB01	AB00[a]		AB00[a]									AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI),

b PK sample must be taken at EOI after flush.

c ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.

In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at EOI + 1 h, +2 h, +4 h, +8 h, +24 h, +48 h and +72 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end of resumed infusion and subsequent samples should be drawn at 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after end of resumed infusion (as per protocol).

ADA: anti-drug antibodies; EOI: End of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: Start of infusion.

1.5.2 All other participants

Cycle	**Cycle 1**				**Cycles 2, 3, 4, 6, 8, 10 + every 4th cycle thereafter**		**EOT visit**
Day	**D1**			**D8**	**D1**		
Time after SAR444245 dosing (EOI, except SOI) [h]	**SOI**	**EOI**	**24**	**168**	**SOI**	**EOI**	**30 (±7) days after last IMP admin**
SAR444245 PK sample		P01[b]	P06			P01[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00
Time after cetuximab dosing (EOI, except SOI) [h]	**SOI**	**EOI**	**24**	**168**	**SOI**	**EOI**	
Cetuximab PK sample	PC00[a]	PC01[b]			PC00[a]	PC01[b]	

a Samples collected strictly before start of infusion (SOI)

b EOI samples = end of infusion samples. Must be taken at end of infusion precisely

c PK sample can be collected at any time during the second day of the cycle.

ADA: anti-drug antibodies, PK: pharmacokinetic: SOI: start of infusion; EOI: end of infusion

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to cohorts with advanced unresectable or metastatic colorectal cancer for the combination therapy with pembrolizumab or cetuximab.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models while anti-PD1 antibody prevents T cell suppression through the PD1/PD-L1 pathway. The combination of anti-PD1 treatment with SAR444245 was tested in a syngeneic mouse CT-26 colon cancer model and induced enhanced anti-tumor activity as demonstrated by an increased number of CR and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

Clinical data from the on-going monotherapy dose escalation of SAR444245 (HAMMER study) has indicated a peripheral increase in the number of NK cells. NK cells are important effector cells which mediate antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab. In vitro data where NK cells pretreated with SAR444245 and then co-cultured with the EGFR-expressing A431 cancer cells improved the ADCC function of cetuximab in a dose-dependent fashion. These data support the evaluation of SAR444245 in combination with cetuximab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the country approved labeling for detailed background information on pembrolizumab.

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD1 has been resolved (7). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (6, 8, 9, 10). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (13, 14, 15, 16, 17, 18, 19). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (7, 16, 18, 19, 20). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (18). Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab IB).

A summary of clinical trial data and the justification of the choice of pembrolizumab dose is provided in Section 4.3.2.

2.2.2 Cetuximab

Cetuximab is an IgG1 monoclonal antibody against the ligand binding domain of epidermal growth factor receptor (EGFR), which is abnormally activated in many epithelial cancers including colorectal cancer (21). The mechanism of action of cetuximab appears to include antibody dependent cell mediated cytotoxicity (22) in addition to EGFR blockade, which may contribute to its efficacy and may be further exploited. Erbitux (cetuximab) is indicated for the treatment of *KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test, as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan, or in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) as the first line treatment, or in combination with irinotecan for patients who are refractory to irinotecan-based chemotherapy. More recently, the BRAF inhibitor encorafenib was approved when combined with cetuximab, for the treatment of mCRC with a *BRAF* V600E mutation, after prior therapy.

2.2.3 Rationale for mCRC and selected populations and experimental SAR444245-based regimens (Cohorts D1 and D2)

Colorectal cancer remains the second leading cause of cancer death, with an estimated 8.7% of cancer-related deaths annually in 2020, and although overall mortality from CRC continues to decline, survival remains poor for advanced disease (23, 24, 25). Chemotherapy and targeted therapies remain the main modalities of treatment.

An increasing number of patients with metastatic colorectal cancer (mCRC) are able to receive 3 or more lines of therapy. Treatments in this setting can include regorafenib (an oral multikinase inhibitor), trifluridine/tipiracil hydrochloride (TAS-102), antibodies that target epidermal growth factor receptor (EGFR) for patients with RAS wild-type tumors (if no prior exposure), and, where approved, ICI for patients with microsatellite instability-high (MSI-H) mCRC (26).

While ICI induce 33%-55% ORR (up to ~65% with nivolumab + ipilimumab in the MSI-H), this population represents <10% of metastatic disease (27), non-MSI-H mCRC remain the majority of the cases and are typically refractory to ICI, being either so-called “cold” [CRC molecular sub-group CMS2&3 - “immune-excluded”] or “immune-restricted” [molecular sub-group CMS4] (28). So beyond the 2L, in non-MSI-H setting, regorafenib and TAS-102 are the two main treatment options. Both regorafenib and TAS-102 have marginal improvement of overall survival (OS_ (6.4 to 8.8 months versus 5.0 to 6.3 months) over BSC or placebo, with minimal impact on PFS (1.9 to 3.2 months versus 1.7 months) and minimal ORR (1-4%) and despite the fact that they have their respective safety profile, they are overall poorly tolerated (29, 30, 31).

Not only is there a strong medical need in that 3L+ mCRC, non-MSI-H population, but it is an opportunity to bring IO in this indication which is known to be refractory to immunomodulatory treatments. Our two hypotheses (exploitation of T cells and NK cells) can be tested in 1) 3L+ patients treated with SAR444245 + pembrolizumab and 2) in 3L+ patients, RASwt (post-cetuximab), treated with SAR444245 + the anti-EGFR IgG1 mAb cetuximab.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Please refer to the master protocol for risk assessment for SAR444245, 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 when combined with either pembrolizumab or cetuximab results from anticipated risks for SAR444245 and from the label information for Keytruda® (pembrolizumab) and Erbitux® (cetuximab), taking into account potential overlapping risks. The available safety data for pembrolizumab and cetuximab, along with proposed mitigation strategies are summarized below and also provided in Table 15.

2.3.1.1 Pembrolizumab

Pembrolizumab potentiates T-cell responses, including antitumor responses, through blockade of PD1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment (TME).

The use of pembrolizumab may cause IRRs (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, and hypersensitivity). Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated adverse events are designated as important identified risks for pembrolizumab (32).

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Among the immune-related AEs (irAEs) associated with pembrolizumab are: immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis, immune-related endocrinopathies, immune-related skin adverse reactions and other additional clinically significant, immune-related adverse reactions (reported in clinical studies or in post-marketing experience): uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, and myelitis.

Efficacy and safety data for pembrolizumab from patients ≥75 years are limited. In this population, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Please refer to the country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for pembrolizumab for more detailed information.

2.3.1.2 Cetuximab

The important identified risks for cetuximab include, but are not limited to: infusion reactions (including anaphylaxis on the first dose); interstitial lung disease, severe adverse skin reactions (with increased risk of secondary bacterial infection), electrolyte disturbances (hypomagnesemia, hypokalemia, hypocalcemia) cardiac adverse events (including cardiopulmonary arrest/sudden death), and eye disorders (including ulcerative keratitis).

The most common adverse reactions (incidence ≥25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The following precautions and warnings are to be acknowledged:

Cetuximab can cause serious and fatal infusion reactions. Infusion reactions of any grade occurred in 8.4% of patients who received cetuximab across clinical trials. Grades 3 and 4 infusion reactions occurred in 2.2% of patients. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion. Premedication with a histamine-1 (H1) receptor antagonist is recommended together with monitor patients for at least 1 hour following each infusion.

Cardiopulmonary arrest or sudden death have occurred in 2-3% patients with squamous cell carcinoma of the head and neck receiving cetuximab with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil. A history of coronary artery disease, congestive heart failure, or arrhythmias and abnormal serum electrolytes may be predisposing factors.

Interstitial lung disease (ILD) that may be fatal has occurred in <0.5% of patients receiving cetuximab in clinical trials.

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of patients across clinical trials. Grades 3 or 4 acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping treatment in

most patients. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis).

Cetuximab can cause hypomagnesemia which occurred in 55% patients in various clinical trials, including Grades 3 and 4 in 6% to 17%. Hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating treatment. It is recommended to monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of treatment and to replete electrolytes as necessary.

Based on animal data and its mechanism of action, cetuximab can cause fetal harm when administered to a pregnant woman. There are no available data for cetuximab exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys resulted in an increased incidence of embryo-lethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development.

The safety and effectiveness of cetuximab in pediatric patients have not been established. The pharmacokinetics of cetuximab, in combination with irinotecan, were evaluated in pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding study. Cetuximab was administered once weekly, at doses up to 250 mg/m^2, to 27 patients ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No new safety signals were identified in pediatric patients. The pharmacokinetics of cetuximab between the two age groups were similar following a single dose of 75 mg/m^2 and 150 mg/m^2. The volume of the distribution appears to be independent of dose and approximates the vascular space of 2 L/m^2 to 3 L/m^2. Following a single dose of 250 mg/m^2, the mean AUC0-inf (CV%) was 17.7 mg*h/mL (34%) in the younger age group (1 - 12 years, n=9) and 13.4 mg*h/mL (38%) in the adolescent group (13-18 years, n=6). The mean half-life of cetuximab was 110 hours (69 to 188 hours) in the younger group and 82 hours (55 to 117 hours) in the adolescent group.

Of the 1662 patients with advanced colorectal cancer who received cetuximab with irinotecan, with FOLFIRI or as monotherapy in six studies, 35% of patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Please refer to the country-approved cetuximab labeling (eg, USPI, SmPC) for more detailed prescribing information.

2.3.1.3 SAR444245 combined with pembrolizumab or cetuximab

Combining SAR444245 with pembrolizumab or cetuximab may lead to an increased frequency and/or severity of adverse events (AEs) related to immune activation or may lead to additional AEs related to immune system activation for each substance individually or may cause occurrences of qualitatively different AEs. Serious adverse drug reactions reported with agents known to increase immune activation include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction (see Section 2.3.1.1). SAR444245 could also increase the incidence of cetuximab-induced cutaneous toxicities.

As all three substances are biologic agents, they may have the propensity to induce infusion-related reactions that may have higher rate of occurrence and severity when SAR444245 with pembrolizumab or cetuximab are used in combination.

The maximum tolerated dose (MTD) of SAR444245 combined with the approved dosing of the anti PD-1 pembrolizumab or cetuximab is under assessment in the HAMMER study using a Q3W schedule. Safety data generated from the combination of SAR444245 and pembrolizumab or cetuximab have informed the selection of the combination dose in this study.

2.3.2 Benefit assessment

More detailed information about the expected benefits of SAR444245 may be found in the master protocol, and the combination of SAR444245 and pembrolizumab or cetuximab are provided below.

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).

Non-MSI-H mCRC are known to not respond to immune checkpoint inhibitors, being qualified as immune excluded or restricted tumors. Combining SAR444245 may unleash inflammatory response in the tumor microenvironment and sensitize CRC to anti-PD1. Preclinical and preliminary clinical data indicates that SAR444245 expands NK cells which are important effector cells mediating antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab. In vitro experiments show that SAR444245 improved the ADCC function of cetuximab in a dose-dependent fashion. The expansion of NK cells induced by SAR444245 may also rescue the activity of cetuximab in *KRAS*wt mCRC. In 3L+ mCRC, the benefit of SoC remains marginal, and the proposed SAR444245-based combination may bring improved benefit compared to SoC.

2.3.3 Overall benefit: risk conclusion

More detailed information about the expected benefits of SAR444245 may be found in the master protocol.

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 pembrolizumab or cetuximab are justified by the anticipated benefits that may be afforded to participants with colorectal cancer.

2.3.4 Benefit and risk assessment in the context of COVID-19 pandemic

Please refer to the master protocol for more details about risks related to the patient population, SAR444245 treatment, and study related activity.

In addition, the impact of PD-1 blockade therapy on Coronavirus disease 2019 (COVID-19) severity was also explored by 2 groups and did not find a clinically meaningful signal (33, 34).

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 2 - Objectives and endpoints

Objectives	Endpoints
Secondary	
• To assess active concentrations of cetuximab when given in combination with SAR444245	• C_{trough} and $C_{end\ of\ infusion}$ of cetuximab
Exploratory	
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Cohorts D1 and *D2* will assess SAR444245 adding on to either pembrolizumab or cetuximab, respectively, in participants with advanced unresectable or metastatic colorectal cancer (mCRC) who have progressed on prior regimens having contained fluoropyrimidine, oxaliplatin, irinotecan, with either bevacizumab or cetuximab, and with no more than 5 prior lines of treatments. Patients are not eligible if MSI-H. Patients with *RASmut* are not eligible for enrollment in Cohort D2.

Please refer to the master protocol for a full description of the study design, and for details applicable to all therapy cohorts.

A graphical presentation of the substudy schema is shown in Figure 1. For treatment period, the completion of Cycle 35 is only applicable for Cohort D1.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that combining the non-alpha-IL2 SAR444245 with either the anti-PD1 antibody pembrolizumab or with the anti-EGFR IgG1 antibody cetuximab will result in a significant increase in the population experiencing an objective response.

The design of the 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, or anti-EGFR therapy as a benchmark to show outstanding objective response rate. The ORR will be assessed using RECIST 1.1 for participants with advanced and metastatic colorectal cancer.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB).
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications. And
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5- fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by

these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.3 Cetuximab dose

This study proposes to evaluate the clinical benefit of 24 µg/kg SAR444245 Q3W combined with the approved dose of 400 mg/m² cetuximab as an IV infusion on day 1 of the study followed by subsequent doses of 250 mg/m² cetuximab IV QW.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohorts D1 and D2 specific criteria.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply (in addition to the criteria listed presented in the master protocol):

Type of participant and disease characteristics

I 01. Histologically or cytologically confirmed diagnosis of colorectal cancer. Only patients with non-MSI-H disease are eligible.

I 02. Confirmed diagnosis at study entry of advanced unresectable or metastatic disease.

Note: *For participants in Cohort D1 and D2*: Disease with any CPS scoring. No need for CPS determination at local laboratory.

I 03. MSI status: Participants must have MSI status known or determined locally and must have non-MSI-H disease to be eligible. Other genetic aberrations: Participants in Cohort D2 must have *RAS* wild-type disease.

I 04. Prior anticancer therapy: Participants should have failed or relapsed on at least 2 but no more than 5 prior regimens having contained fluoropyrimidine, oxaliplatin, irinotecan, with bevacizumab and/or cetuximab.

I 05. Provision of tumor tissue:

- **Mandatory baseline biopsy** for participants in **Cohorts D1, and D2**: minimum 5 slides with 4-5 micron thickness for the first 20 participants who have signed ICF (excluding screen failure participants), minimum 10 slides with 4-5 micron thickness for subsequent participants in each cohort. Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- **Mandatory on-treatment biopsy** for at least 20 participants in each of **Cohort D1 and Cohort D2,** if clinically feasible. On-treatment biopsies are otherwise **optional** per Investigator's discretion and evaluation of all other participants.
- 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.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply (in addition to the criteria listed in the master protocol):

Medical conditions

E 01. Electrolyte (magnesium, calcium, potassium) levels outside of normal ranges for participants in Cohort D2.

Prior/concomitant therapy

E 02. *For participants in Cohort D1*. - Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD-1/PD-L1 but have written confirmation they were on control arm are allowed).

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

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

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

For study treatment duration, completion of Cycle 35 is only applicable for Cohort D1.

Dosing sequence for Cohort D1: [redacted]

Enrolled participants in Cohort D2 will receive treatment with both SAR444245 and cetuximab until PD.

Dosing sequence for Cohort D2: [redacted]

In addition, if a participant has immune unconfirmed progression of disease (iUPD) and is clinically stable, it is at the discretion of the Investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed (iCPD) at least 4 weeks, but no longer than 8 weeks from the date of the scan suggesting progression of disease (Section 10.9).

6.1.1 Investigational medicinal product (IMP)

Investigation medicinal product is defined as SAR444245, pembrolizumab, and cetuximab administered in combination as described in Section 4. 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 for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 3 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab	Cetuximab
Type	See master protocol	Biologic	Biologic
Dose formulation	See master protocol	Solution for infusion	Solution for injection
Unit dose strength(s)	See master protocol	100 mg/vial	As per locally approved formulation
Dosage level(s)[a]	24 µg/kg Q3W	200 mg Q3W	An initial loading dose of 400 mg/m^2 on C1D1, followed by 250 mg/m^2 once weekly
Route of administration	See master protocol	IV infusion	IV infusion
Use	See master protocol	Treatment of cancer (combination)	Treatment of cancer (combination)
IMP or NIMP	See master protocol	IMP	IMP
Packaging and labeling	See master protocol	Supplied in single dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.	To be locally sourced as locally available/marketed where possible. Central sourcing (EU sourced and clinically labeled only for the countries where local sourcing is not possible)
Current/Former name(s) or alias(es)	See master protocol	Keytruda	As per locally approved formulation

a See master protocol.

6.1.2 Non-investigational medicinal products

Non-investigational medicinal products include the premedication administered for SAR444245 and cetuximab.

For Cohort D1, in case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, SAR444245 premedication no longer needs to be administered.

6.1.2.1 Premedication for SAR444245

Please refer to the master protocol.

6.1.2.2 Premedication for cetuximab

All participants who will receive cetuximab should be premedicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions (IRs).

[redacted]

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

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications for SAR444245 and cetuximab are permitted. according to the guidelines described in this section. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

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, Day 1 should be delayed for all IMPs) is permitted in case of treatment-emergent adverse event (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.

In participants who have SAR444245 dose reduction due to SAR444245 related Grade ≥3 treatment-related adverse events (TRAEs), SAR444245 dose may be re-escalated to ■ µg/kg if:

- no SAR444245 related Grade ≥3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND
- both Investigator and Sponsor agree that the participant has clinical benefit.

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 of the master protocol 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 all IMP components are permanently discontinued, it is full permanent discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.5.2 Cycle delay

The treatment window is ±3 days for each of the Q3W administrations. The treatment window is ±1 day for cetuximab administration on Day 8 and Day 15 of each cycle.

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 the next dose after recovery from the toxicity as described in Section 6.5.3 and Section 6.5.4. After cycle is delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline.

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.
- For cetuximab Day 8 and Day 15 administration in each cycle: if toxicity occurs and the patient does not recover on the day of planned infusion or within the following 3 days, infusion may be omitted.
- In case of cycle delay or dose omissions 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 or a dose omission, it is per Investigator's decision to restart the study treatment.
  - After a cycle delay of >14 days and ≤84 days, or 2 to 4 consecutive dose omissions, it is per Investigator's decision to restart the study treatment or the IMP that is omitted, 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, or if the participant has more than 4 consecutive dose omissions.
  - For any delayed cetuximab treatment, do not repeat the initial dose of 400 mg/m². At the restart of cetuximab treatment, all subsequent infusions will be at the appropriate dose level according to Table 4.
- Cycle delay or dose omission may be considered 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 delay or omission, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for the delay or omission should be documented in the participant's study record.

Modification of dose levels in case of dose reduction

Dose reduction steps for cetuximab are shown in Table 4. One or several doses of cetuximab can be omitted.

Table 4 - Dose levels for cetuximab dose reduction

Starting dose	Dose level 1	Dose level 2
400 mg/m^2 then 250 mg/m^2	200 mg/m^2 (20% decrease)	150 mg/m^2 (20% decrease)

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

Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 5-11) will be required to temporarily cycle delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline.

The dose of SAR444245 should be reduced to [redacted]µg/kg (with the exception of lymphocytopenia which is directly associated with SAR444245 mode-of-action and does not require dose reduction) in cases of:

- First occurrence of Grade 3 TRAE that does not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 TRAE of any duration.
- Grade 4 TRAE.
- First occurrence of Grade 3 laboratory abnormality that are clinically significant per Section 10.3.1 of the master protocol. and that do not resolve to Grade 1 or baseline within 72 hours, and second occurrence of Grade 3 clinically significant laboratory abnormality of any duration.
- Grade 4 laboratory abnormalities that are clinically significant.

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

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

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.

Recommended guidelines for the management of specific adverse events including irAE, CRS, Vascular Leak Syndrome (VLS) and Infusion-related reactions (IRR) are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as adverse events of special interest (AESIs), depending on grading according to National Cancer Institute- Common Terminology Criteria for Adverse Event (NCI-CTCAE) V5.0 (see Section 8.3.8 of the master protocol). In case a specific adverse event meets the AESI definition it must be documented in the e-CRF.

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol 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.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 5.

After an infusion-related reaction due to pembrolizumab infusion (Grade 3 or Grade 4), the SAR444245 infusion will be delayed and can be administered after resolution of symptoms. The Investigator should discuss with the Sponsor's Medical Monitor if the SAR444245 infusion needs to be delayed more than 1 day.

Guidelines for the management of SAR444245 IRR events are provided in Table 6. 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, please see Section 6.1.2.1 of the master protocol.

Table 5 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - Epinephrine*, - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics, - Oxygen, - Pressors, - Corticosteroids. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Table 6 - SAR444245 infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE 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 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	SAR444245 infusion should be interrupted if applicable. If symptoms resolve within 1 hour of interrupting 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 should be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. The next infusion should be given 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 (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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.
Grade 4 Life-threatening; pressor or ventilator support indicated	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination 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 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; NCI = National Cancer Institute; NSAIDs: nonsteroidal anti-inflammatory drugs.

Participants who experience cetuximab-related infusion reactions should have cetuximab reduced according to Table 7 and continue to receive antihistamine premedication prior to administration. Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it should remain decreased for all subsequent infusions. If the participant experiences a second infusion reaction at the decreased rate, cetuximab should be permanently discontinued. If any Grade 3-4 infusion reaction occurs, cetuximab treatment should be discontinued immediately.

Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions.

Table 7 - Cetuximab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Dose modification
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop cetuximab infusion and administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity and monitor closely for any worsening.
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	Stop the cetuximab infusion immediately, administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Cetuximab should permanently discontinued. The participant can continue treatment with SAR444245.

Abbreviations: CTCAE = Common terminology criteria for adverse events; IRR = Infusion related reaction; NCI = National Cancer Institute.

6.5.4.2 Anaphylaxis

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of SAR444245, pembrolizumab and cetuximab being administered.

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) (36, 1, 37).

6.5.4.3 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 V5.0 and managed according to institutional standards.

Cetuximab may be associated with CRS. CRS typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion of cetuximab. Cetuximab related IRR's, including CRS, are discussed in Section 6.5.4.1. Please refer to Table 7 for Cetuximab IRR dose modifications and treatment guidelines.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 8. 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 C-reactive protein (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 according to severity grading are provided in Table 8. ASTCT CRS consensus grading scale is provided in Section 10.11 of the master protocol.

Table 8 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] 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 participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during 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. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants 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. SAR444245 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.	Stop cetuximab infusion and administer bronchodilators, oxygen, etc., as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity and monitor closely for any worsening.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS grade 3, SAR444245 should be temporarily cycle delayed, and subsequent treatment should be resumed only when symptoms have resolved or improved to Grade 1 at [redacted] µg/kg or permanently discontinued, as clinically indicated. If CRS Grade 4, SAR444245 should be permanently discontinued, as clinically indicated. If CRS Grade 3 or Grade 4, IV corticosteroids should be initiated (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.	Stop the cetuximab infusion immediately, administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Cetuximab should permanently discontinued. The participant can continue treatment with SAR444245.

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
	If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants 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 should be discussed with clinical site specialists	

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b 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.

c 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.

d 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: 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; IL = Interleukin; IMP=investigational medicinal product; IV = Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.5.4.4 Immune-related adverse events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. IrAEs are thought to be caused by unrestrained cellular immune responses directed at the normal host tissues. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing pembrolizumab clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care.

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 severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 9. Of note, when study interventions are administered in combination, 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.

The CTCAE V5.0 must be used to grade the severity of AEs.

When pembrolizumab can be restarted, it should be administered at the initial planned dose and schedule as no modification is allowed:

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 9, the combination of SAR444245 and pembrolizumab or cetuximab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 9 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab and SAR444245 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab and SAR444245 have been withheld, pembrolizumab and SAR444245 may be resumed after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold[a]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue[b]		
Diarrhea/Colitis	Grade 2 or 3	Withhold[a]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis 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.
AST or ALT elevation or Increased Bilirubin	Grade 2[c]	Withhold[a]	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
	Grade 3[d] or 4[e]	Permanently discontinue[b]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a,f]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold[a]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold[a] or permanently discontinue[b,f]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold[a] or permanently discontinue[b,f]		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Neurological Toxicities	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
All Other immune-related AEs	Persistent Grade 2	Withhold[a]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold[a] or discontinue based on the event[g]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		

a SAR444245 to be withheld plus pembrolizumab to be withheld corresponds to “cycle delay”.

b Permanently discontinuation of full study treatment.

c AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal.

d AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal.

e AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.

f The decision to withhold or permanently discontinue pembrolizumab and/or SAR444245 is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab and SAR444245 may be resumed.

g Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) 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 10.11 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab should only be used in the context of CRS, as outlined in Table 10. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 10 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 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.	SAR444245[a] should be delayed. Treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted] µg/kg 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. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 3 ICANS, SAR444245 should be delayed. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted]µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. If Grade 4 ICANS, both SAR444245 and pembrolizumab should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 8 in Section 6.5.4.3. 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, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants 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 clinical specialists should be involved whenever indicated.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; ICANS= Immune effector cell associated neurotoxicity syndrome; ICE= Immune Effector Cell-Associated Encephalopathy; IV = Intravenous.

6.5.4.6 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 11. 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 (38).

Table 11 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	SAR444245 should be delayed. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. 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. In participants 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 Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AKI= acute kidney injury; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; MW= molecular weight; NCI = National Cancer Institute; VLS= vascular leak syndrome.

6.5.4.7 Dermatologic toxicity

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis.

The dosing of cetuximab will be omitted 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. If acneiform rash improves during this time, then the dose of cetuximab should be reduced as indicated in Table 12. The dose modification guidelines as per the current local label should be followed for dermatologic toxicities other than acneiform rash.

If acneiform rash does not improve during this time, cetuximab will be permanently discontinued.

Participant who have held cetuximab therapy for more than 2 consecutive infusions due to acneiform rash, and upon resolution of the toxicity are still felt to be benefiting from cetuximab treatment may resume cetuximab with Sponsor approval.

Table 12 - Cetuximab dose modification for dermatologic toxicities

Dermatologic toxicities and infectious sequelae (eg, acneiform rash, mucocutaneous disease)	Recommended cetuximab dose modification
1st occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, continue at the same dose of 250 mg/m^2. If no improvement, discontinue cetuximab.
2nd occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, permanently reduce at 200 mg/m^2. If no improvement, discontinue cetuximab.
3rd occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, permanently reduce at 150 mg/m^2. If no improvement, discontinue cetuximab.
4th occurrence; Grade 3 or 4	Permanently discontinue cetuximab.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for definition and treatment of SAR444245 overdose.

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. There is no specific antidote for overdose with pembrolizumab, or cetuximab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol and Section 1.3.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

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

Please refer to the master protocol for RECIST 1.1.

[redacted]

8.2 SAFETY ASSESSMENTS

Please refer to the master protocol.

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

Please refer to the master protocol.

In addition, combining SAR444245 with other anticancer therapies may increase the frequency and severity of immune-related adverse events related to other anticancer therapies. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level will be monitored for participants in Cohort D1.

8.3.1 Time period and frequency for collecting AE and SAE information.

Please refer to the master protocol for AEs and serious adverse events (SAEs) collection. For participants in Cohort D1 irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

For pembrolizumab and cetuximab, SAEs that are considered expected will be specified in the reference safety information (country-approved product labeling for pembrolizumab).

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Please refer to the master protocol.

In addition, symptomatic or asymptomatic overdose with pembrolizumab are described as below:

- An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol for a description of common PK evaluations. Substudy specific evaluations are summarized below.

PK parameters (eg, maximum concentration, area under the concentration time curve) will be generated in patients undergoing intensive PK sampling (as in Section 1.5.1 of the master protocol). Samples collected for analyses of cetuximab 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 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

The plan is to treat approximately 40 participants per cohort for Cohorts D1 and D2.

Table 13 lists estimated ORR and 90% exact confidence intervals (CIs) by number of responders from a sample size of 40 participants treated.

Table 13 - Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
2	5% (0.9% - 14.9%)
4	10% (3.5% - 21.4%)
6	15% (6.7% - 27.5%)
8	20% (10.4% - 33.2%)
10	25% (14.2% - 38.7%)
12	30% (18.3% - 44.0%)
14	35% (22.6% - 49.2%)

CI: confidence interval; N=number.

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 these cohorts.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

Please refer to the master protocol.

9.4.3 Secondary endpoint(s)

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

9.4.3.1 Other secondary endpoints

Plasma concentrations (or where applicable PK parameters) of cetuximab will be summarized with descriptive statistics.

9.4.4 Tertiary/exploratory endpoint(s)

[redacted].

9.4.4.1 Exploratory antitumor indicators

[redacted]

9.4.5 Other safety analysis

Please refer to the master protocol.

9.4.6 Other analysis

Please refer to the master protocol.

9.5 INTERIM ANALYSES

Please refer to the master protocol.

For each cohort, if the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5% for both cohorts) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

Please refer to the master protocol.

10.1.2 Financial disclosure

Please refer to the master protocol.

10.1.3 Informed consent process

Please refer to the master protocol.

10.1.4 Data protection

Please refer to the master protocol.

10.1.5 Committees structure

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

Please refer to the master protocol.

10.1.7 Data quality assurance

Please refer to the master protocol.

10.1.8 Source documents

Please refer to the master protocol.

10.1.9 Study and site start and closure

Please refer to the master protocol.

10.1.10 Publication policy

Please refer to the master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort D1 and D2 specific evaluations are presented in Table 14.

Table 14 - Protocol-required laboratory tests

Endocrine function tests[a]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

NOTES :

a Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT in cohorts receiving pembrolizumab. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

In addition, for participants in Cohort D2, electrolytes to be done weekly under treatment and then at the end of treatment, at FU visit 1 and as clinically indicated. After last IMP administration, additional electrolytes monitoring for Cohort D2, outside the visits, may be done according to the local standard institutional care.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

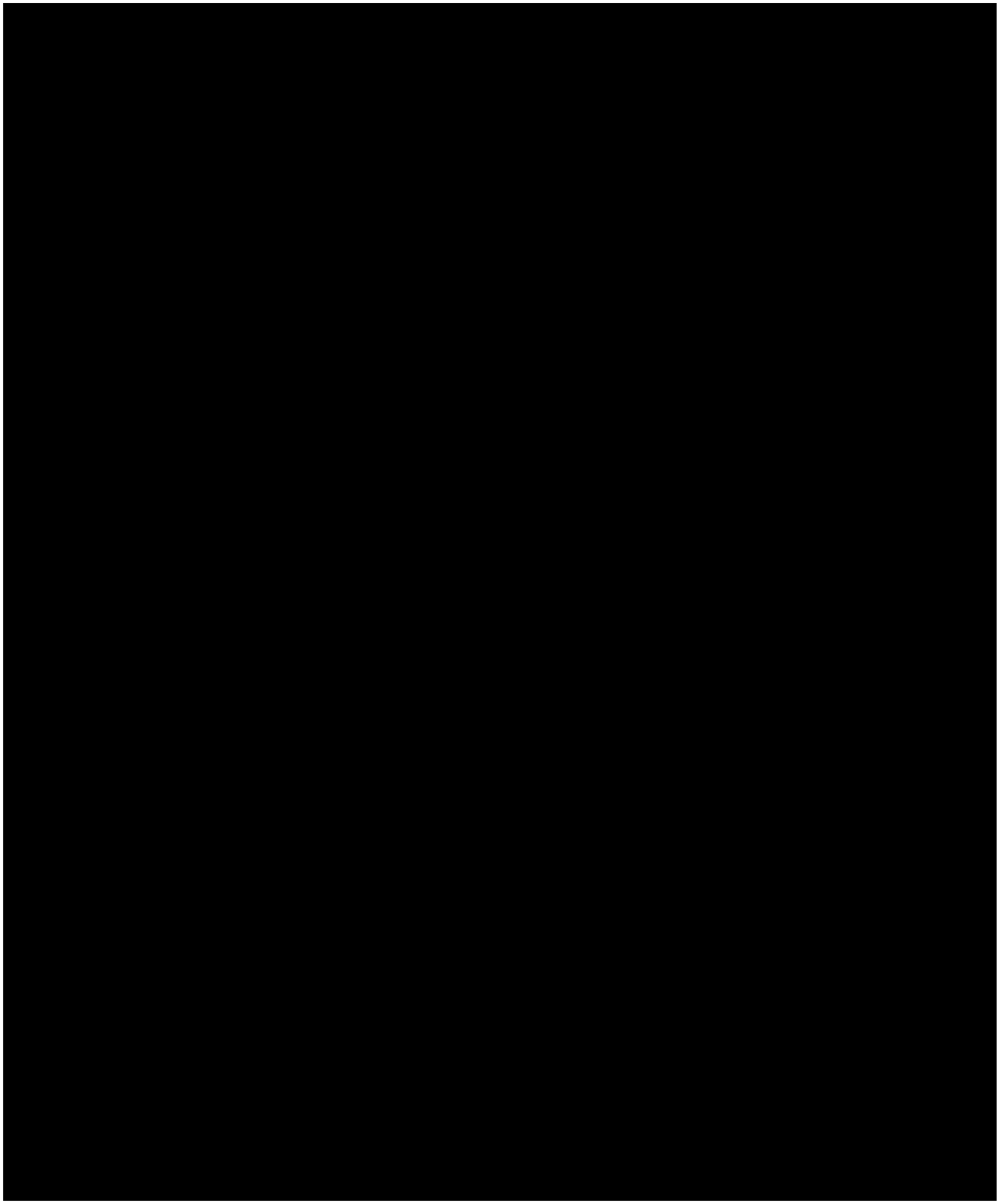
Please refer to the master protocol.

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

Please refer to the master protocol.

10.9 APPENDIX 9: [redacted]

[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 or [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. 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: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Please refer to the master protocol.

10.11 APPENDIX 11: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245, available information about pembrolizumab and cetuximab is shown in Table 15.

Table 15 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome. Cetuximab Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. Symptoms may include bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed. Anaphylactic reactions may occur as early as within a few minutes of the first infusion and can occur despite the use of premedication. The risk for anaphylactic reactions is much increased in patients with a history of allergy to red meat or tick bites or positive results of tests for IgE antibodies against cetuximab (α-1-3-galactose). In these patients cetuximab should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well-trained personnel with resuscitation equipment ready. A cytokine release syndrome (CRS) typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion. Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnea that occur in a close temporal relationship mainly to the first cetuximab infusion	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion associated reactions are provided in Table 5. Cetuximab Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms or signs of an infusion-related reaction occur. The first dose should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have performed IgE antibodies before a subsequent infusion is given. Premedicate with a histamine-1 (H1) receptor antagonist prior to cetuximab administration. Monitor patients for at least 1 hour following each cetuximab infusion, in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Initiate SAR444245 infusion only when no infusion reaction has occurred after 1-2 hours of observation. In patients requiring treatment for infusion reactions, use recommended per the country-approved product labeling (eg, USPI, SmPC) for cetuximab. If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		a) Grade 1: continue slow infusion under close supervision b) Grade 2: continue slow infusion and immediately administer treatment for symptoms c) Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions. A close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease
Immunogenicity (Anti-drug antibodies)	Cetuximab The development of human anti-chimeric antibodies (HACA) is a class effect of monoclonal chimeric antibodies. Current data on the development of HACAs is limited. Overall, measurable HACA titers were noted in 3.4% of the patients studied, with incidences ranging from 0% to 9.6% in the target indication studies. No conclusive data on the neutralizing effect of HACAs on cetuximab is available to date. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other undesirable effect to cetuximab.	
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported but included among infusion-related reactions in label. Cetuximab Please see above within Infusion reactions	Exclusion of participants with known hypersensitivity to any components of pembrolizumab. Also, see specific instructions for cetuximab.
Infections	Pembrolizumab Common: pneumonia. Cetuximab Patients who receive cetuximab in combination with platinum-based chemotherapy are at an increased risk for the occurrence of severe neutropenia, which may lead to subsequent infectious complications such as febrile neutropenia, pneumonia or sepsis. Careful monitoring is recommended in such patients, in particular in those who experience skin	See routine mitigation in the master protocol.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	lesions, mucositis or diarrhea that may facilitate the occurrence of infections. Further, the risk for secondary infections (mainly bacterial) of adverse skin reactions is increased and cases of staphylococcal scalded skin syndrome, necrotizing fasciitis and sepsis, in some cases with fatal outcome, have been reported	
Hepatotoxicity	Pembrolizumab Hepatitis occurred in 0.8% of patients, including Grade 2, 3 or 4 cases in 0.1%, 0.5% and 0.1% patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.6 months (range 8 days to 21.4 months). The median duration was 1.1 months (range 1 day to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 0.3% patients. Hepatitis resolved in 36 patients. Cetuximab Increase in liver enzymes is very common	Exclusion of participants with impaired liver functions. 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 9.
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury Cetuximab Not reported in the SmPC	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 9.
Hypomagnesaemia	Cetuximab Hypomagnesaemia is very common	Exclusion of participants with electrolytes (magnesium, calcium, potassium) outside the normal ranges. Monitor electrolytes regularly as per protocol.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy Uncommon: epilepsy. Cetuximab: Headaches are common	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 9. Analgesics as clinically indicated
Cardiovascular effects, including QT interval prolongation	Cetuximab Cardiopulmonary arrest or sudden death have occurred in 2-3% patients with squamous cell carcinoma of the head and neck receiving cetuximab with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil cetuximab. A history of coronary artery disease, congestive heart failure, or arrhythmias and abnormal serum electrolytes may be predisposing factors.	Specifically, for patients receiving cetuximab, exclude patients with electrolytes (magnesium, calcium and potassium) <LLN and monitor serum electrolytes weekly during and for at least 8 weeks after last cetuximab administration.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab. Cetuximab Not reported as such in the SmPC.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 9. Patients treated with cetuximab: If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. Very rarely, Stevens-Johnson syndrome/toxic epidermal necrolysis may occur in patients treated with cetuximab.	interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Cetuximab should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.
Interstitial lung disease	Cases of interstitial lung disease (ILD), including fatal cases, have been reported, with the majority of patients from the Japanese population. Confounding or contributing factors, such as concomitant chemotherapy known to be associated with ILD, and pre-existing pulmonary diseases were frequent in fatal cases.	Patients treated with cetuximab: Patients should be closely monitored for ILD. In the event of symptoms (such as dyspnoea, cough, fever) or radiographic findings suggestive of ILD, prompt diagnostic investigation should occur.
Dermatological toxicities	Pembrolizumab: Refer to immune-related adverse events Cetuximab: Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of patients across clinical trials. Grades 3 or 4 acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping treatment in most patients. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis).	For cetuximab: Monitor patients for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during cetuximab therapy. Withhold, reduce dose or permanently discontinue cetuximab based on severity of acneiform rash or mucocutaneous disease
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab. Cetuximab EGFR is involved in foetal development. Limited observations in animals are indicative of a placental transfer of cetuximab, and other IgG1 antibodies have been found to cross the placental barrier. Animal data revealed no evidence of teratogenicity. However, dependent on the dose, an increased	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly. It is recommended that women do not breast-feed during treatment with cetuximab and for 2 months after the last dose, because it is not known whether cetuximab is excreted in breast milk.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	incidence of abortion was observed. Sufficient data from pregnant or lactating women are not available. It is strongly recommended that cetuximab be given during pregnancy or to any woman not employing adequate contraception only if the potential benefit for the mother justifies a potential risk to the foetus. Breast-feeding It is recommended that women do not breast-feed during treatment with cetuximab and for 2 months after the last dose, because it is not known whether cetuximab is excreted in breast milk. Fertility There are no data on the effect of cetuximab on human fertility. Effects on male and female fertility have not been evaluated within formal animal studies.	
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.8 of the master protocol.

10.12 APPENDIX 12: ASTCT ASSESSMENT FOR ICANS AND CRS

Please refer to the master protocol.

10.13 APPENDIX 13: ABBREVIATIONS

AESIs: adverse events of special interest
ASTCT: American Society for Transplantation and Cellular Therapy
CR: complete response
[redacted]
e-CRF: electronic case report form
EOT: end of treatment
ICANS: immune Cell-Associated Neurotoxicity Syndrome
ICU: intensive care unit
[redacted]
IRR: infusion-related reactions
mCRC: metastatic colorectal cancer
NCI-CTCAE: National Cancer Institute- Common Terminology Criteria for Adverse Event
NHP: non-human primate
[redacted]
PD1: programmed cell death protein 1
[redacted]
PK: pharmacokinetic

SAEs: serious adverse events
TEAE: treatment-emergent adverse event
TIL: tumor infiltrating lymphocytes
VLS: Vascular Leak Syndrome

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

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

10.14.1 Amended protocol 01 (30 August 2021)

This amended protocol (Amendment 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 overall rationale for the amendment is to include stopping rules for futility and update the rules for dose modification in case of treatment-related adverse events (TRAEs) for Cohorts D1 and D2 in substudy 04.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.5 Pharmacokinetics flowcharts	The frequency of sampling for cetuximab PK sample has been increased to obtain data every cycle for the first 3 cycles, every other cycle for 4 cycles, then every 4th cycle.	Regulatory Authorities (FDA) request to generate more comprehensive evidence
Section 5.1 Inclusion Criteria	For I03, "Participants in Cohort D2" has been added to clarify that the genetic aberration of the RAS wild type disease is only applicable on the D2 cohort.	For clarity
	In I06, "- less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "-less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment".	Harmonization per program level approach
Section 6.5.1 General rules	The following sentence has been deleted "Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.", and the following sentences have been added "In participants who have SAR444245 dose reduction due to SAR444245 related Grade ≥3 TRAEs, SAR444245 dose may be re-escalated to[redacted] µg/kg if: ·no SAR444245 related Grade ≥3 TRAE or clinically significant laboratory abnormality within at least 2 subsequent cycles, AND ·both Investigator and Sponsor agree that the participant has	For clarification of how dose will be reduced and re-escalated for participants who experience any Grade ≥3 TRAEs

Section # and Name	Description of Change	Brief Rationale
	clinical benefit.".	
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following sentence "Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) will be required to temporarily delay the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy." has been changed to "Participants who experience Grade ≥3 TRAEs at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) not listed in Section 6.5.4 (Tables 5-11) will be required to temporarily delay the IMP. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline". Dose reduction rules have added, and the following sentence has been deleted "Dose reduction for SAR444245 from [redacted]µg/kg to [redacted] µg/kg (or another lower recommended dose) may be decided when specified in the protocol or following discussions with the Sponsor."	For consistency and clarity
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 6 under Grade 3 and Grade 4, and in Table 7 under Grade 3 or 4, "prematurely" has been removed from "prematurely permanently discontinued".	For clarity
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 5 under Grade 3, the following sentence was deleted "If subsequent administration is tolerated, increasing the SAR444245 dose to[redacted]µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor".	For consistency
Section 6.5.4.7 Dermatologic toxicity	The following sentence "The dose modification guidelines in Table 4 should be followed…" has been changed to "The dose modification guidelines as per current local label should be followed…".	For clarity
Section 6.5.4.7 Dermatologic toxicity	In Table 12, "dose level 1" has been changed to "200 mg/m^2", "dose level 2" has been changed to "150 mg/m^2". In Table 12 under Grade 3 or 4, "prematurely" has been removed from "prematurely permanently discontinue cetuximab".	For clarity
Section 9.5 Interim analyses	The following sentences have been added "For each cohort, if the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5% for both cohorts) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis."	To include stopping rules for futility

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