AMENDED CLINICAL TRIAL PROTOCOL 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 other anticancer therapies for the treatment of participants with lung cancer or pleural mesothelioma**
Protocol number:	**ACT16849**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with other anticancer therapies for the treatment of participants with lung cancer or mesothelioma**
Acronym	**Pegathor Lung 202**
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	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	ALL	20 Oct 2021, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 02	ALL	05 May 2021, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 01	ALL	19 Mar 2021, version 1 (electronic 1.0)
Original Protocol		23 Feb 2021, version 1 (electronic 2.0)

Amended protocol 03 (20 Oct 2021)

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

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for the amendment is in response to Health Authorities' (HAs) requests for correction and clarification. Instructions regarding participant enrollment specific to France as requested by the French HA (ANSM) have been added. 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	The study acronym "Pegathor Lung 202" was added.	For consistency across the program.
1.1 Synopsis: Table 2 Objectives and Endpoints, 3 Objectives and Endpoints, 9.4.3.1 Time to response, and 9.4.3.2 Duration of response	Definitions of secondary endpoints "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 CR that is subsequently confirmed and determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma). • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until progressive disease (PD) determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for	For clarification

Section # and Name	Description of Change	Brief Rationale
	mesothelioma) or death from any cause, whichever occurs first.	
1.1 Synopsis, 4.1 Overall Design, 9.4.3.3 Progression-free survival, and 9.5 Interim analyses	The cut-off date for the final analysis was defined. The study cut-off date has been replaced by cohort cut-off for final analysis.	For clarification
1.1 Synopsis, Figure 1, 1.3 Schedule of Activities (SoA), 4.1 Overall Design	The "Study Committee" has been renamed as "Study Board" and its composition and role have been clarified in Section 4.1.	For consistency with Sanofi standard terminology
1.1 Synopsis, 6.1.2.1 Premedication for SAR444245, Table 23 Risk assessment	[redacted]	
1.1 Synopsis, 6.1.2.1 Premedication for SAR444245	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 administration route to be used.
1.3 Schedule of Activities (SoA)	Footnote f now applies only to C1D15 and was changed from: C1D8 and/or C1D15 visits must be performed on site only for participants enrolled in the Safety run-in, participants scheduled to have blood draws for biomarker assessment on Day 8 or ADA on Day 15, and participants in Cohort B2 who will receive nab-paclitaxel administration on Day 8. 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. The Study Committee may decide to cancel safety assessment on C1D8 and C1D15, upon agreement with Sponsor, and if justified by safety data. to C1D15 visits must be performed for participants enrolled in the safety run-in. For all other participants, the Study Board may decide to cancel safety assessment on C1D15, upon agreement with Sponsor, and if justified by safety data.	To limit visits and operational procedures for participants' comfort.
1.3 Schedule of Activities (SoA)	Footnote r was added: For carboplatin/cisplatin dosing, only in Cycles 3 and 4.	For clarification
1.5.1 All cohorts	The ADA sample at C1D15 was replaced with a sample at C1D8.	The C1D15 visit may be cancelled by the study board as described above, and a sample at C1D8 is considered

Section # and Name	Description of Change	Brief Rationale
		sufficient to detect the potential early onset of an ADA response.
2.3.1.5 SAR444245 combined with pembrolizumab and SAR444245 combined with pembrolizumab and chemotherapy regimen, 2.3.2 Benefit assessment	A description of the benefit-risk assessment of SAR444245 combined with pembrolizumab and chemotherapy has been added. The section title was changed from "SAR444245 combined with pembrolizumab" to "SAR444245 combined with pembrolizumab and SAR444245 combined with pembrolizumab and chemotherapy regimen".	To complete the benefit-risk assessment and to respond to HA request (Italy)
4.3.1 SAR444245 dose	This section was updated with the most recent data available from Phase 1 Hammer study.	To include all available data in support of the safety of the recommended phase 2 dose.
5 Study population	The following text has been added “For participants enrolled in France and Japan please refer to Section 10.7”.	To address HA requests (France and Japan)
5.1 Inclusion Criteria	In I 04 the timeline for the archival tumor tissue sample was changed from “collected more than 6 months prior to screening” to “collected more than 6 months prior to first IMP administration”.	For clarification
5.1 Inclusion Criteria	In I 06, for participants in Cohorts B1 and B2, the wording has been changed to; -Patients with metastatic NSCLC should have progressed after having received prior benefit from an anti-PD1/PD-L1* containing regimen (SD, partial response [PR], or CR). Patients must have received prior anti-PD1/PD-L1 containing regimen given concurrently or sequentially with a platinum-based chemotherapy. Patients who received concurrent anti-PD1/PD-L1 chemotherapy combination are allowed to receive one additional chemotherapy. Platinum ineligible patients can enroll after anti-PD1/PD-L1 monotherapy, or anti-PD1/PD-L1 monotherapy followed by a non-platinum form of chemotherapy. *If anti-PD1/PD-L1 was used beyond initial radiological progression while continuing to use the same anti-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.	To clarify requirements for the prior lines of treatment for Cohorts B1 and B2
5.1 Inclusion criteria, 8.2.5 Pregnancy testing, 8.3.5 Pregnancy, Table 21 footnote e	In I 08, the recommended duration for continuing contraception after last dose of study intervention in Cohort A3 was changed from 420 days to 330 days for male participants and from 330 days to 420 days for female participants.	For correction, as the original presentation inadvertently reversed the information for males and females.
	For female participants in cohorts A1, A2, B1, B2 and C1 (SAR444245 plus pembrolizumab), the recommended	For correction

Section # and Name	Description of Change	Brief Rationale
	duration for continuing contraception after last dose of study intervention was changed from 180 days to 150 days.	
5.2 Exclusion criteria	E 04 was changed from "History of allogenic or solid organ transplant" to "History of allogenic tissue/solid organ transplant".	For clarification
5.2 Exclusion criteria	E 21 was changed from "Known hypersensitivity to or contraindication for the use of any study intervention, including premedication to be administered in this study, as well as PEG or any pegylated drug" to "Known hypersensitivity to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein".	To clarify that patients with known hypersensitivity to any excipient of the study interventions or to E. coli-derived protein must be excluded
5.2 Exclusion criteria and 6.5.2 Prohibited concomitant medications, Appendix 12 Risk assessment Table 23	E 25 [redacted] has been deleted. The following sentence in Section 6.5.2 has been deleted: "[redacted]." In Table 23, the row for [redacted] was deleted.	Based on new de-risking in-vitro data
5.2 Exclusion criteria	E 29 was 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 has used 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 was added "A participant may be rescreened only once".	For clarity
6.2 Preparation/handling/ storage/accountability	The following text regarding DTP shipment of IMP was deleted: "(except for DTP shipment, for which a courier company has been approved by the Sponsor)".	Direct-to-patient shipment of IMP is not possible in this study.
6.6.2 Cycle delay and dose omission and 6.6.3 General guidelines for the management of	The following text regarding the treatment resumption after cycle delay/treatment withhold was deleted: "or is stable and manageable through supportive/medical therapy".	For correction

Section # and Name	Description of Change	Brief Rationale
treatment-related adverse events		
6.6.4.2 Dose modification for nab-paclitaxel	Table 11 - Recommended nab-paclitaxel dose reductions for non-hematological toxicities, was added	To comply with nab-paclitaxel dosing instructions and to respond to HA request (Italy)
6.6.5.1 Infusion-related reactions (IRR)	In Table 13, the language regarding SAR444245 dose modification guidelines was modified as follows: For Grade 2 events "SAR444245 infusion should be interrupted if applicable" was changed to "Interrupt SAR444245 infusion" For Grade 3 and 4 events: "SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, permanently discontinue SAR444245." was changed to "Permanently discontinue SAR444245."	For clarification
6.6.5.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 14, the dose modification instructions for events of CRS were modified as follows: For Grade 3 events the following text was deleted: [redacted] For Grade 4 events, the following text was deleted: "as clinically indicated".	For consistency with instructions given in Section 6.6.1 General rules
6.6.5.5 Immune cell-associated neurotoxicity syndrome (ICANS)	In Table 16, instructions for treatment with IV corticosteroids were added for Grade 3 events.	For consistency with instructions for Grade 4 events.
6.6.5.6 Vascular leak syndrome	The literature reference cited was changed to: Siddall E, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int. 2017 Jul;92(1):37-46. Crossreferences to articles cited thereafter have been renumbered accordingly.	For correction
8.3.1 Time period and frequency for collecting AE and SAE information	The instruction to stop collecting AE and SAE information should the participant initiate another anticancer therapy was removed. All AEs and SAEs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards
[redacted]	[redacted]	[redacted] standards
9.3 Populations for Analyses	The efficacy population description was revised to "Efficacy population will include all participants from the exposed population with at least one evaluable post-	To characterize efficacy excluding newly enrolled participants

Section # and Name	Description of Change	Brief Rationale
	baseline tumor assessment or who permanently discontinued study treatment".	
9.4.1 General considerations	"By dose (as applicable)" has been added to efficacy analyses.	For clarification
9.4.3.6 Clinical laboratory evaluations and 9.4.5 Other safety analyse(s)	Descriptive statistics for laboratory variables and vital signs will be performed only when relevant. The following text was deleted: "These analyses will be performed using local measurements for laboratory variables".	These analyses will be done as needed following analyses of abnormalities according to NCI-CTCAE grade
9.4.5 Other safety analyse(s)	"ECG" was removed from quantitative analyses.	ECG data are not collected systematically during the treatment period
Appendix 10.1.3 Informed Consent Process	Minor revisions were made to the paragraph describing consent for the use of participants' data or biological samples for future research.	For clarification and closer alignment with the informed consent form
[redacted]	[redacted]	[redacted]
Appendix 10.7 Country specific requirements	Instructions regarding participant enrollment specific to France were added.	To respond to HA requests (France)
	Specific tests for early detection of interstitial lung disease have been added at Screening for participants in Japan.	To respond to HA requests (Japan)
10.8 Appendix 8: Response evaluation criteria in solid tumors (RECIST) 1.1	In the following sentence "Confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response or progressive disease", the text "or progressive disease" was deleted.	To correct a typographical error
10.12 Appendix 12 Risk assessment	The following text was added "For pembrolizumab, the information below is per currently available USPI and EU SmPC. Please always refer to the latest version of the SAR444245 IB and pembrolizumab local label for the most up-to-date safety data".	For clarification
10.12 Appendix 12 Risk assessment, Table 23	In Table 23, assessment for hepatoxicity with pembrolizumab was revised to be aligned with the latest version of USPI warnings and precautions for pembrolizumab.	For consistency with latest available information
Throughout the document	The term "Infusion-associated reaction (IAR)" was changed to "infusion-related reaction (IRR)"	For consistency with MedDRA definition
Throughout the document	Minor editorial updates.	For clarity and consistency

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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 lung cancer or pleural mesothelioma

Brief title: A study of SAR444245 combined with other anticancer therapies for the treatment of participants with lung cancer or mesothelioma

Rationale:

SAR444245, with its site-specific pegylation, was designed to substantially reduce association with the interleukin (IL)-2 α receptor, while retaining stimulatory activity for cells expressing the moderate affinity IL-2 βγ receptor. Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and non-human primate (NHP) models while anti-PD1 antibody prevents T cell suppression through the programmed cell death-1/programmed cell death-ligand 1 (PD1/PD-L1) pathway. The combination of anti-PD1 treatment with SAR444245 was tested in the syngeneic murine colon cancer Ct-26 model and induced enhanced anti-tumor activity 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 anti-PD1 monoclonal antibody pembrolizumab with the non-alpha IL-2 SAR444245, with or without chemotherapy, will result in a significant increase in the percentage of patients with lung cancer or pleural mesothelioma experiencing an objective response rate (ORR).

Table 1 provides an overview by study intervention, disease type, and primary tumor assessment criteria of the different cohorts that will be assessed in the study.

Table 1 - Overview of study cohorts

Cohort	Study intervention	Disease	Primary tumor assessment criteria
A1	SAR444245 + pembrolizumab as 1L therapy	NSCLC, PD-L1 TPS ≥50%	RECIST 1.1
A2	SAR444245 + pembrolizumab as 1L therapy	NSCLC, PD-L1 TPS 1%-49%	RECIST 1.1
A3	SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin as 1L therapy	Non-squamous NSCLC	RECIST 1.1
B1	SAR444245 + pembrolizumab as 2/3L therapy	NSCLC	RECIST 1.1
B2	SAR444245 + pembrolizumab + nab-paclitaxel as 2/3L therapy	NSCLC	RECIST 1.1
C1	SAR444245 + pembrolizumab as 2/3L therapy	Mesothelioma	mRECIST

1L = First-line; 2/3L = Second- or third-line; mRECIST = Modified response evaluation criteria in solid tumors; NSCLC = Non-small cell lung cancer; PD-L1 = Programmed cell death-ligand 1; RECIST = Response evaluation criteria in solid tumors; TPS = Tumor proportion score.

Objectives and endpoints

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with other anticancer therapies (see Table 1 for the description of study cohorts).	• Objective response rate defined as the proportion of participants who have a confirmed CR or partial response (PR) determined by investigator, per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (1) for Cohort A1, Cohort A2, Cohort A3, Cohort B1 and Cohort B2; per modified RECIST (mRECIST) (2) for Cohort C1.
Secondary	
• To confirm the dose and to assess the safety profile of SAR444245 when combined with other anticancer therapies.	• Incidence of TEAEs, dose-limiting toxicities (DLT), SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus gradings (3).
• 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 (for NSCLC) or mRECIST (for mesothelioma). • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until progressive disease (PD) determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma) 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 for NSCLC or mRECIST for mesothelioma). • 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 (for NSCLC) or mRECIST (for mesothelioma) or death due to any cause, whichever occurs first.
• To assess the plasma concentrations of SAR444245 when given in combination with pembrolizumab.	• Plasma concentrations of SAR444245.
• To assess the immunogenicity of SAR444245.	• Incidence of anti-drug antibodies (ADAs) against SAR444245.

Objectives	Endpoints
Exploratory	
[redacted]	

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 lung cancer or mesothelioma.

Brief summary

Cohort A1, Cohort A2 and **Cohort A3** will assess the antitumor efficacy and safety of adding SAR444245 to therapeutic approaches with documented efficacy profile as 1L non-small cell lung cancer (NSCLC) therapy. Participants with previously untreated Stage IV NSCLC will be enrolled sequentially based on histology and PD-L1 tumor proportion score (TPS**)** to Cohort A1, Cohort A2 and Cohort A3.

- **Cohort A1**: participants with PD-L1 TPS ≥50% NSCLC, to receive SAR444245 + pembrolizumab as 1L therapy.
- **Cohort A2**: participants with PD-L1 TPS 1%-49% NSCLC, to receive SAR444245 + pembrolizumab as 1L therapy.

- **Cohort A3**: participants with non-squamous NSCLC, to receive SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin as 1L therapy.

Cohort B1 and **Cohort B2** will assess SAR444245-based therapies as 2/3L NSCLC therapy when receiving standard of care (SOC) is not in the best interest of participants or where no SOC is established.

- **Cohort B1**: participants with NSCLC, to receive SAR444245 + pembrolizumab as 2/3L therapy.
- **Cohort B2:** participants with NSCLC, to receive SAR444245 + pembrolizumab + nab-paclitaxel as 2/3L therapy.

Cohort C1 will evaluate SAR444245-based therapy as 2/3L mesothelioma treatment where no SOC is well established. Participants with mesothelioma who have experienced disease progression during or after at least 1 but no more than 2 prior regimens (detailed in Section 5.1 Inclusion Criteria I 06) will be enrolled

- **Cohort C1**: participants with mesothelioma, to receive SAR444245 + pembrolizumab as 2/3L therapy.

The study consists of a safety run-in and core phase for all 6 cohorts, and an expansion phase for Cohorts B1 and/or B2. In the core phase approximately 40 participants at the confirmed safe dose will be enrolled per cohort. The results of an interim analysis will decide if the expansion phase will be opened for Cohorts B1 and/or B2. Approximately 57 additional participants are planned to be enrolled in each cohort in the expansion phase in order to better assess antitumor activity.
A graphical presentation of the study schema is shown in Figure 1.

A safety run-in will confirm the dose of SAR444245 in each regimen tested in this study, namely: **SAR444245 + pembrolizumab; SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin; SAR444245 + pembrolizumab + nab-paclitaxel**. Participants who fulfill the eligibility criteria of any cohort testing the regimen may be enrolled to the safety run-in of that regimen. Participants will be enrolled across Cohorts A1, A2, B1 and C1 to receive SAR444245 and pembrolizumab. Enrollment will be paused once at least 6 participants are evaluable for DLT. Safety data for these participants will be reviewed by a Study Board (SB) comprising Investigators or designees participating in the safety run-in part of applicable cohorts and the Sponsor clinical team members. DLT-evaluable participants include all treated participants in the safety run-in who have been observed for at least 21 days. Any participant who experienced a DLT during the first 21 days will also be DLT-evaluable. If no safety concerns are identified by the SB, participant enrollment will continue for the 4 cohorts. If after recruiting the first 10 participants there are fewer than 6 participants evaluable for DLT, more participants will be enrolled to ensure at least 6 DLT evaluable participants after agreement from SB. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants in the core phase for that specific cohort (for example, if 3 Cohort A1 participants are enrolled in the safety run-in and treated at the confirmed safe dose, approximately 37 additional participants will be enrolled into Cohort A1 to have the total number of 40 participants).

The safety run-in for other regimens (**ie, SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin; and SAR444245 + pembrolizumab + nab-paclitaxel**) will not be opened until the SAR444245 + pembrolizumab dose is confirmed, and enrollment of Cohort A2 and Cohort B1, respectively, is completed. Details of the opening sequence of the different cohorts are described below.

The SAR444245 dose to be confirmed is 24 µg/kg, administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle). Overall safety monitoring will be performed throughout the study. If recommended by the SB, SAR444245 dose level may be reduced to [redacted] or another lower dose level which will be explored following the same process described in the safety run-in for 24 µg/kg dose level.

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

Dose limiting toxicity: Selected events occurring during the DLT observation period (21 days of first cycle) are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245. Please refer to the full list of events in Section 4.1. Based on the occurrence of DLT and overall assessment of safety data supplemented with data from other SAR444245 studies, the SB will determine if the dose of SAR444245 needs to be reduced to [redacted] or another lower dose level, in agreement with the Sponsor.

Safety run-in and core phase enrollment sequence

SAR444245 and pembrolizumab - Cohorts A1, A2, B1 and C1

As the safety run-in of this regimen is opened first, Cohorts A1, A2, B1 and C1 will be the initial cohorts to enroll.

SAR444245, pembrolizumab, pemetrexed, and carboplatin/cisplatin - Cohort A3

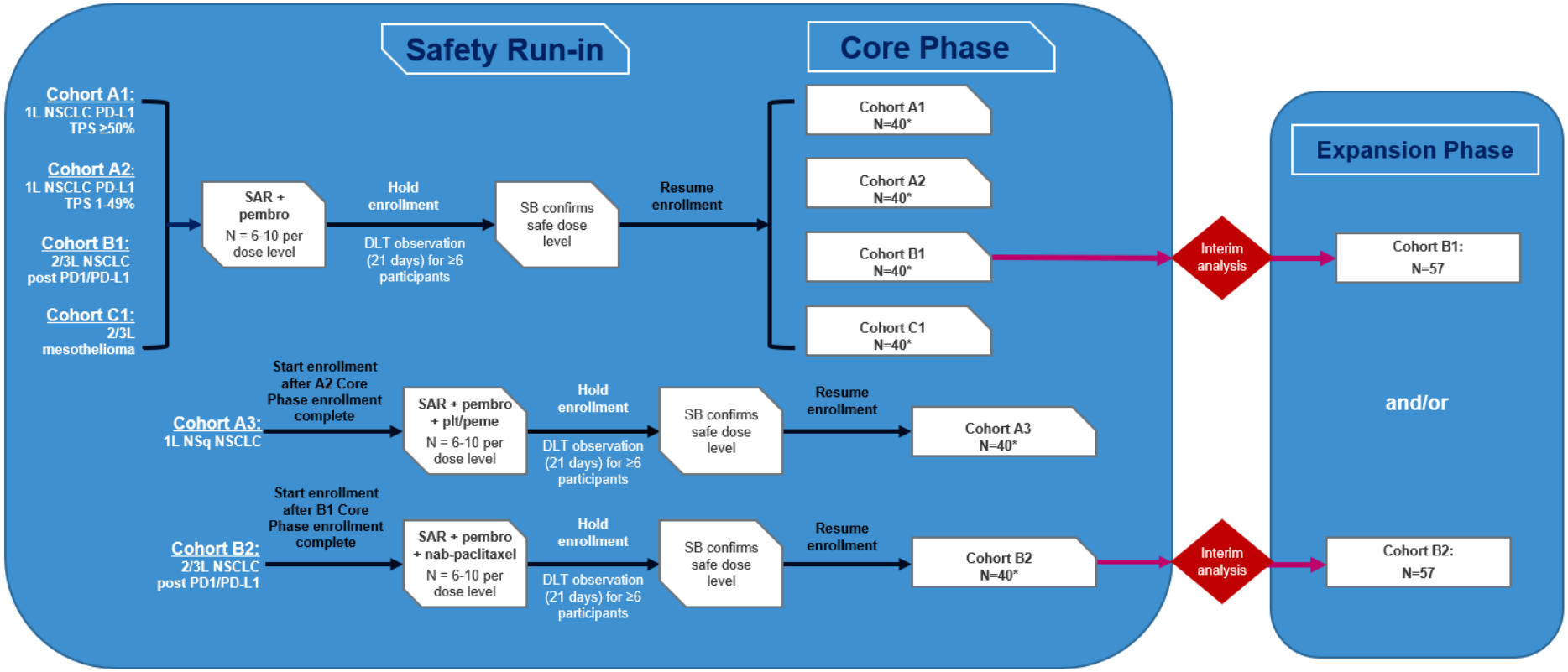
Once enrollment is completed for Cohort A2, the safety run-in of Cohort A3 can be conducted, with up to 10 participants enrolled to receive SAR444245, pembrolizumab, pemetrexed, and carboplatin/cisplatin prior to an enrollment pause. If Cohort A1 is still enrolling when Cohort A3 is opened, a participant who is eligible for both Cohorts A1 and A3 should be enrolled in Cohort A1 until Cohort A1 enrollment is completed.

SAR444245, pembrolizumab, and nab-paclitaxel - Cohort B2

Once enrollment is completed for Cohort B1, the safety run-in of Cohort B2 can be conducted, with up to 10 participants enrolled to receive SAR444245, pembrolizumab, and nab-paclitaxel prior to an enrollment pause.

Additional cohorts with different regimens or indications may be added to this protocol.

Figure 1 - Overall study schema



*Total number in Core Phase including patients in Safety Run-in at the confirmed safe dose

1L: First-line; 2/3L: Second- or third-line; NSCLC: Non-small cell lung cancer; NSq: Non-squamous; pembro: pembrolizumab; PD1/PD-L1: Programmed cell death 1/ ligand 1; Plt: carboplatin/cisplatin; peme: pemetrexed; SB: Study Board; SAR: SAR444245; TPS: Tumor proportion score.

Special considerations pertaining to methodology

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

Number of participants:

Overall in the core phase (all cohorts), approximately 40 participants will be enrolled and treated at the confirmed safe dose per cohort.

In the expansion phase (Cohorts B1 and/or B2), approximately 57 participants will be enrolled and treated at the confirmed safe dose per cohort.

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), other full permanent discontinuation criteria as described in Section 7, or completion of Cycle 35 (for Cohorts, A1, A2, B1, B2 and C1).
- **End of Treatment and Follow-up:** End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **End of Treatment (EOT)**:
    1. Participants who discontinue study treatment **without radiological or clinical PD** or who **complete 35 cycles of treatment without PD** (per RECIST 1.1 or mRECIST), 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 radiological or clinical PD** (per RECIST 1.1 or mRECIST) **or** [redacted] ([redacted]) will be followed in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-Up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. 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 final cohort cut-off, or upon cancellation of Survival Follow-up at the discretion of the Sponsor at any prior timepoint.

For Cohort A1, Cohort A2, Cohort A3 and Cohort C1, the cohort cut-off for the primary ORR endpoint analyses is estimated to be approximately 9 months from the date of the last participant's first infusion in the core phase (to document that last participant response is maintained for 6 months in the core phase).

For Cohort B1 and Cohort B2, the cohort cut-offs for the analyses are as follows:

- Interim analysis cut-off: the date on which all participants in the core phase have at least 2 post-baseline tumor assessments with response durability demonstrated or discontinue study treatment (whichever occurs first).
- Primary analysis cut-off: the date on which the last participant response is maintained for 6 months in the expansion phase (approximately 9 months from last participant's first infusion in the expansion phase).

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 will be 3 years from the date of cohort last-patient-in, or when all patients within the cohort have completed the study.

Study interventions

Cohort A1 (NSCLC PD-L1 TPS ≥50%, SAR444245 + pembrolizumab as 1L therapy)

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

- Formulation: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-use vial with an extractable volume of 1mL.
- Route of administration : IV infusion.
- Dose regimen: 24 µg/kg (or reduced to [redacted] or another lower dose level recommended by SB) administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles**.

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

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, preferably 30 to 60 minutes prior to SAR444245 infusion (ideally no longer than 60 minutes) for the first 4 cycles:

- Acetaminophen (paracetamol) 650 to 1000 mg IV or oral route (PO), and then optionally thereafter as needed.
- Diphenhydramine 25 to 50 mg IV or PO (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter as needed.

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 the next cycle. If no IRR is observed for the next cycle without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during the next cycle without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent 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 A2 (PD-L1 TPS 1%-49% NSCLC, SAR444245 + pembrolizumab as 1L therapy)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab and SAR444245, as described for Cohort A1.

Noninvestigational medicinal products

Premedication for SAR444245, as described for Cohort A1.

Cohort A3 (non-squamous NSCLC, SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin as 1L therapy)

Dosing sequence: [redacted]

For timing of pemetrexed premedication, please refer to the specific section below.

Investigational medicinal products

Pembrolizumab and SAR444245, as described for Cohort A1.

Pemetrexed

Pemetrexed will be administered [redacted]

- Formulation: pemetrexed is a concentrate for solution for infusion supplied in 100 mg/4 mL (25 mg/mL) solution in single-dose vials (or any other formulation approved locally).
- Route of administration: IV infusion.
- Dose regimen: pemetrexed will be administered on Day 1 of each 21-day cycle as a 500 mg/m^2 IV infusion over approximately 10 mins until PD or unacceptable toxicity.

Cisplatin

Cisplatin will be administered [redacted] and administered according to local practice and labels.

- Formulation: cisplatin 1 mg/mL sterile concentrate for solution for infusion supplied in single-dose vials (or any other formulation approved locally).

- Route of administration : IV infusion.
- Dose regimen: 75 mg/m^2 IV infusion administered according to locally approved label for **4 cycles** on Day 1 of each cycle.

Carboplatin

Carboplatin will be administered [redacted] as per local practice and labels.

- Formulation: carboplatin 10 mg/mL (or any other formulation approved locally).
- Route of administration : IV infusion.
- Dose regimen: AUC of 5 IV infusion over 15-60 min on Day 1 for **4 cycles** on Day 1 of each cycle.

Noninvestigational medicinal products

Premedication for SAR444245, as described for Cohort A1.

Premedication for pemetrexed

All participants should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below:

- Folic acid 350-1000 µg oral: At least 5 daily doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg intramuscular injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1-4 but not to exceed doses in MASCC (Multinational Association for Supportive Care in Cancer) guidelines (5).

Cohort B1 (NSCLC, SAR444245 + pembrolizumab as 2/3L therapy)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab and SAR444245, as described for Cohort A1.

Noninvestigational medicinal products

Premedication for SAR444245, as described for Cohort A1.

Cohort B2 (NSCLC, SAR444245 + pembrolizumab + nab-paclitaxel as 2/3L therapy)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab and SAR444245, as described for Cohort A1.

Nab-paclitaxel

- Formulation: nab-paclitaxel (powder for suspension for infusion [or any other formulation approved locally]).
- Route of administration: IV infusion.
- Dose regimen: nab-paclitaxel will be administered as a 100 mg/m^2 IV infusion over 30 mins on Days 1 and 8 of each cycle for **6 cycles**.

Noninvestigational medicinal products

Premedication for SAR444245, as described for Cohort A.

Cohort C1 (mesothelioma, SAR444245 + pembrolizumab as 2/3L therapy)

Dosing sequence: [redacted]

Investigational medicinal products

Pembrolizumab and SAR444245, as described for Cohort A1.

Noninvestigational medicinal products

Premedication for SAR444245, as described for Cohort A1.

Statistical considerations:

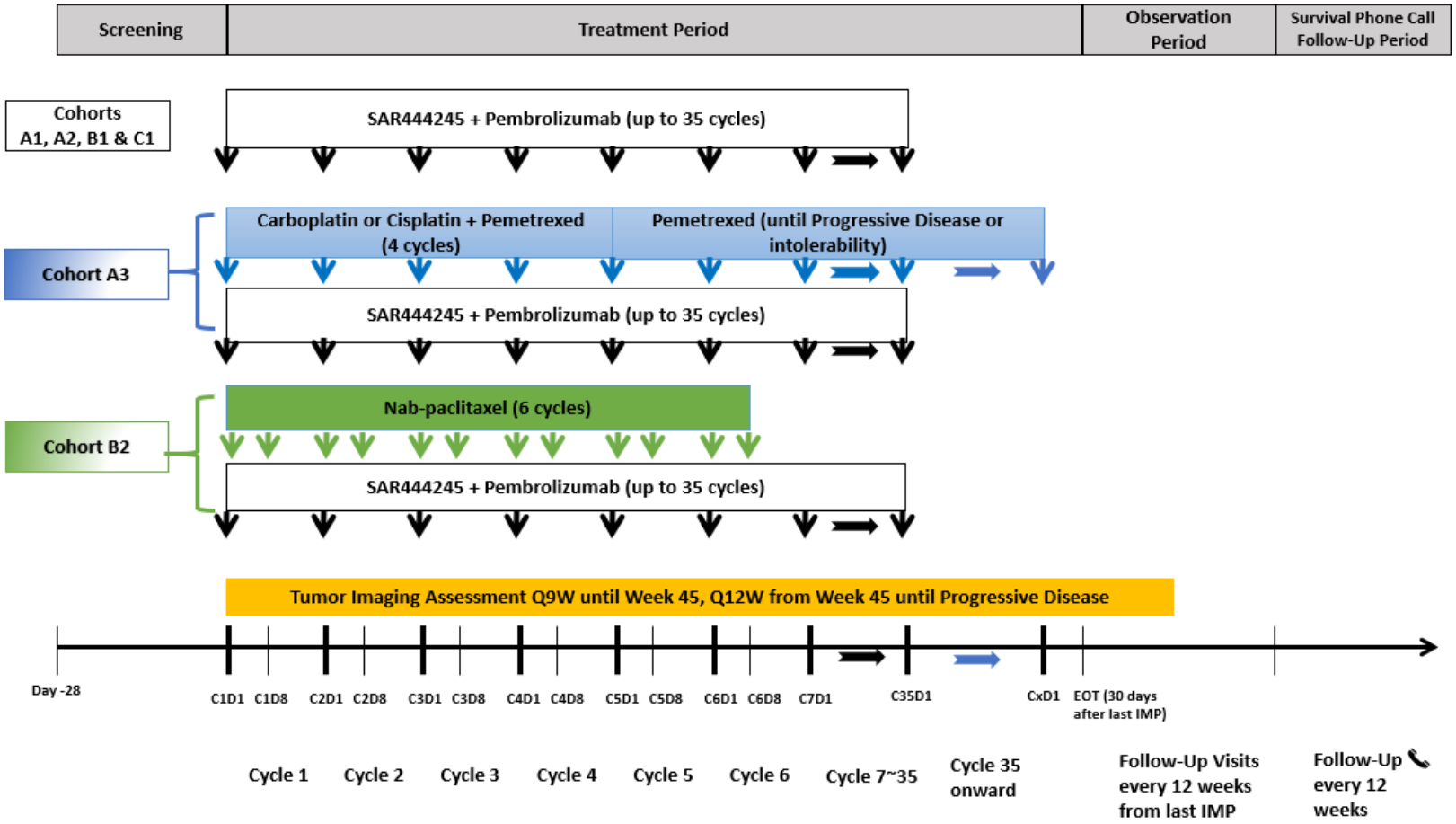
- **Analysis of primary endpoint:**
  - Objective response rate (ORR) and best overall response (BOR) will be summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for ORR will be computed using the Clopper-Pearson method.

- **Analysis of secondary efficacy endpoints:**
  - The TTR will be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
  - The DoR will only be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
  - The CBR will be estimated by dividing the number of participants with clinical benefit by the number of participants in the efficacy population.
  - The PFS will be summarized on the efficacy population using Kaplan-Meier methods. The median PFS times and associated 90% CI will be provided.
- **Analysis of secondary safety endpoints:**
  - Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by primary System Organ Class and Preferred Term (PT) will be summarized by NCI-CTCAE V5.0 grade (all grades and Grade ≥3) for the exposed population. Similar summaries will be prepared for TEAEs related to SAR444245 and those related to other IMP components, TEAEs leading to permanent partial intervention discontinuation (any of the IMP components), TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) and participants who died by study period (treatment, post-treatment) 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 V5.0, 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 SAR444245 will be summarized with descriptive statistics by each cohort.

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

1.2 SCHEMA

Figure 2 - Graphical study design



C = Study cycle (1 cycle = 21 days); D = Study day; EOT End of treatment; FU = Follow up; Q9W = Every 9 weeks; Q12W = Every 12 weeks; IMP = Investigational product.

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening	Treatment period[b]										End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
Evaluation[a]		Cycle 1					Cycle 2		Cycle 3-6		Cycle 7-35	Cycle 36 and beyond	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone call Follow-up	
Cycle day (Visit window in Days)	D-28 to D-1	D1	D2	D3[e]	D8 (±1)	D15[f] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D1 (±3)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) from last IMP admin	6 months (±7 days) from last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Informed consent/ Inclusion/Exclusion criteria	X																	
IRT contact	X	X					X		X		X	X	X					
Demography, medical/surgical and disease history	X																	See Section 8
Performance status (ECOG)	X	X			X	X	X		X		X	X	X	X				
Body weight/ Height[h]	X	X					X		X		X	X						
Full physical examination	X												X					

	Screening	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
Evaluation[a]		Cycle 1					Cycle 2		Cycle 3-6		Cycle 7-35	Cycle 36 and beyond	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone call Follow-up	
Cycle day (Visit window in Days)	D-28 to D-1	D1	D2	D3[e]	D8 (±1)	D15[f] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D1 (±3)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) from last IMP admin	6 months (±7 days) from last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Directed physical examination		X	X	X	X	X	X	X[f]	X	X[f]	X	X		X				See Section 8.2.1
Vital signs	X	X	X	X	X	X	X	X[f]	X	X[f]	X	X	X	X				See Section 8.2.2
SpO_2	X																	
Laboratory and other investigations																		
12-Lead ECG	X	As clinically indicated																See Section 8.2.3
LVEF	X	As clinically indicated																See Section 8.2.3
Pregnancy test	X	X					X		X		X	X	X	X	X			See Section 8.3.5 and Section 10.2
Blood chemistry/ hematology	X	X	X	X	X	X	X		X		X	X	X	X				See Section 10.2

	Screening	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
Evaluation[a]		Cycle 1					Cycle 2		Cycle 3-6		Cycle 7-35	Cycle 36 and beyond	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone call Follow-up	
Cycle day (Visit window in Days)	D-28 to D-1	D1	D2	D3[e]	D8 (±1)	D15[f] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D1 (±3)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) from last IMP admin	6 months (±7 days) from last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
T3, FT4, TSH and cortisol[i]	X						X		X		X	X	X	X				See Section 10.2
Coagulation	X	As clinically indicated																See Section 10.2
Urinalysis[j]	X	X							X		X	X	X	X				See Section 10.2
Hepatitis serology, CD4 counts and viral load	X	As clinically indicated																See Section 10.2
IMP		X			X[k]		X	X[k]	X[r]	X[k]	X	X[l]						
Prior Medication	X																	
Hospitalization[m]		X																
AE/SAE assessment[n]	X	Continuous throughout treatment period												X				See Section 8.3
Concomitant Meds	X	Continuous throughout treatment period																See Section 6.5

	Screening	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
Evaluation[a]		Cycle 1					Cycle 2		Cycle 3-6		Cycle 7-35	Cycle 36 and beyond	EOT Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Phone call Follow-up	
Cycle day (Visit window in Days)	D-28 to D-1	D1	D2	D3[e]	D8 (±1)	D15[f] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D8[g] (±1)	D1 (±3)	D1 (±3)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) from last IMP admin	6 months (±7 days) from last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
First subsequent anticancer therapy													X	X	X	X	X	
Survival status																	X	
Pharmacokinetic (PK) / Pharmacodynamic (PDy)/Immunogenicity assessments																		
PK	See PK Flow-Chart in Section 1.5																	
ADA																		
PDy - Blood and tumor tissue collection[o]	See Biomarkers Flow-Chart in Section 1.4																	

	Screening	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
Evaluation[a]		**Cycle 1**					**Cycle 2**		**Cycle 3-6**		**Cycle 7-35**	**Cycle 36 and beyond**	**EOT Visit**	**Follow-up Visit 1**	**Follow-up Visit 2**	**Follow-up Visit 3 and beyond**	**Phone call Follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[e]**	**D8 (±1)**	**D15[f] (±1)**	**D1 (±3)**	**D8[g] (±1)**	**D1 (±3)**	**D8[g] (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP admin or prior to initiation of further therapy**	**3 months (±7 days) from last IMP admin**	**6 months (±7 days) from last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Tumor assessment																		
CT/MRI[p]	X								X		X	X	X	X	X	X		See Section 8.1.1
Brain imaging[q]	X																	See Section 8.1.1

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. Baseline evaluations should be completed within 7 days prior to the first dose of IMP, except for tumor assessment that may be performed within 28 days prior to IMP administration, and unless specified otherwise. There is no need to perform Cycle 1 Day 1 laboratory assessments that have been performed as part of screening within 3 days prior to 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. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the study.

e Visit and assessments on C1D3 are only for participants in the safety run-in.

f C1D15 visits must be performed for participants enrolled in the safety run-in. For all other participants, the Study Board may decide to cancel safety assessment on C1D15, upon agreement with Sponsor, and if justified by safety data.

g Only for Cohort B2.

h 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.

i 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.

j Urinalysis will be performed every 4 cycles during Treatment Period and as clinically indicated.

k Nab-paclitaxel dosing on Days 1 and 8 of each cycle for 6 cycles, only for Cohort B2.

l Only for pemetrexed.

m Only for safety run-in participants. See requirements specific to Japan in Section 10.7.

n 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 (3).

o If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Tumor biopsy during treatment period should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

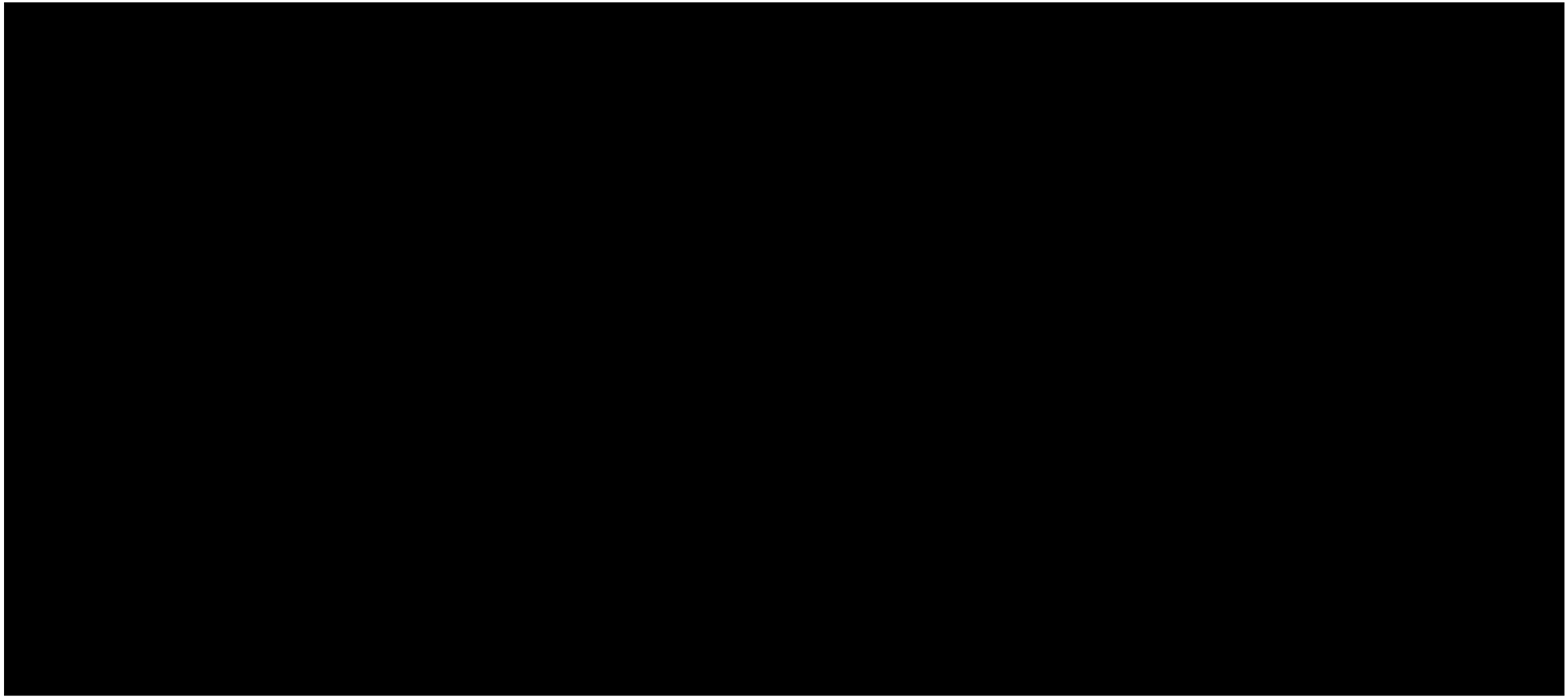
p CT/MRI: The initial tumor imaging will be performed within 28 days prior to C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will 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. 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.

q 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. Participants 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. 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 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 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.

r For carboplatin/cisplatin dosing, only in Cycles 3 and 4.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; C = Cycle; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-treatment; FT4 = free thyroxine; FU = Follow-up visit; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; ICF = informed consent form; IMP = investigational medicinal product; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; PD = progressive disease; PDy = pharmacodynamic; PK = pharmacokinetic; PR = partial response; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; mRECIST = Modified RECIST; SAE = serious adverse event; SpO_2: oxygen saturation; TSH = thyroid stimulating hormone.

1.4 BIOMARKER FLOWCHART



1.5 PHARMACOKINETIC FLOWCHART

The sampling time-points for PK and ADA for/against SAR444245 and/or other IMPs may be updated during the course of the study based on the updated knowledge of drug behavior and upon notification from the Sponsor. See requirements specific to Japan in Section 10.7.

1.5.1 All cohorts

Cycle	Treatment Cycle 1					Treatment Cycle 2, 4, 7, 10 + every 5th cycle		EOT visit
Day	D1		D2	D3[a]	D8	D1		
Time after start of SAR444245 dosing	SOI	EOI	At any time	At any time	At any time	SOI	EOI	30 (±7) days after last IMP administration
SAR444245 PK sample ID		P00[b]	P01	P02			P00[b]	
SAR444245 ADA sample ID	AB00[c]				AB01	AB00[c]		ABF00

a Day 3 sampling only for participants in the safety run-in who have a Day 3 visit
b PK sample must be taken at EOI after flush
c Samples collected strictly before start of infusion (SOI)

Abbreviations: ADA: anti-drug antibodies; D: day; EOT: end of treatment; PK: pharmacokinetic.

2 INTRODUCTION

SAR444245 is a recombinant human IL-2 with a site-specific substitution of a non-native azido lysine amino acid residue which is bio-conjugated to a single linear 30 kDa PEG. SAR444245 is being developed as an immuno-oncology treatment to be administered every 2 weeks (Q2W) or less frequently (every 3 weeks [Q3W] in the present study) in patients with cancer. [redacted]. The site-specific pegylation of IL-2 in SAR444245 provides a "non alpha" pharmacologic profile for SAR444245 that is designed to prevent engagement of the high affinity IL-2Rα, while maintaining CD8+ T cell anti-tumor activity and resulting in an improved safety profile relative to aldesleukin. Aldesleukin is approved in the United States (US) for the following indications: the treatment of metastatic renal cell carcinoma (RCC) and metastatic melanoma, with the same or limited approval status in other countries. Its use has resulted in durable CR in some patients with anti-tumor effects via elevations in CD8+ T cells (naïve, effector, and memory T cells). However, widespread use of aldesleukin is limited by its low response rate, short half-life ($t_{1/2}$), 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 natural killer (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 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 demonstrated enhanced anti-tumor activity and prolonged survival compared to each 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. For more details on specific indications refer to the pembrolizumab Investigator's Brochure (IB).

Refer to the 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 (6). 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, and 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 (7, 8).

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) (9, 10).

The structure of murine PD1 has been resolved (11). 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 (10, 12, 13, 14). 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 (15, 16).

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 (17, 18, 19, 20, 21, 22, 23). 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 (11, 20, 22, 23, 24). 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 (22). 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 the pembrolizumab IB).

A summary of clinical trial data and the justification of the choice of pembrolizumab dose is provided in Section 4.3.1.

2.2.2 Rationale for NSCLC and selected participant population (Cohorts A1, A2, A3, B1 and B2)

Worldwide, lung cancer remains the leading cause of cancer incidence and its mortality is projected to reach 2.45 million worldwide by 2030, a 39% increase in just over a decade (25). NSCLC accounts for approximately 85% of all lung cancer cases, with 2 broad histologic subtypes, squamous cell carcinoma and non-squamous cell carcinoma (majority is adenocarcinoma) (26).

2.2.3 Current standard of care in NSCLC

2.2.3.1 PD1/PD-L1 inhibitor monotherapy or in combination with chemotherapy as first-line therapy

Prominent adaptive antitumor immune responses have been documented by direct analysis of immune cell populations and indirectly by measuring tumor PD-L1 expression, interferon gamma–related signatures, or multimarker transcriptomic profiles (27, 28, 29, 30). Using immunohistochemistry (IHC), PD-L1 expression in greater than or equal to 1% of tumor cells has been reported in approximately 60% of advanced NSCLC and with high levels (eg, ≥50% of tumor cells) in 25% to 30% of cases (31, 32). Analysis of specific T-cell populations reveals that NSCLC tumors contain higher CD3+ TILs, CD8+ cytotoxic cells, and CD8+/CD45R0+ effector memory cells than non-tumor lung (33, 34, 35, 36, 37). Elevated levels of these T-cell subsets have been consistently associated with better outcomes, confirming their antitumor nature (38, 39).

The KEYNOTE 024 trial reported a significant improvement in overall survival (OS) for pembrolizumab monotherapy in an equally selected population, mostly generated in the subgroup of patients with high PD-L1 expression (≥50%) (40). In the KEYNOTE 042 trial, a significant benefit with 1L pembrolizumab compared with platinum-based chemotherapy was revealed by

using a lower selection threshold, PD-L1 ≥1% (41). The KEYNOTE 021 trial was the first Phase 2 randomized study reporting improved outcome (ORR: 56.7% versus 30.2%; PFS: 24.0 months versus 9.3 months; and OS: not reached versus 21.0 months) with upfront pembrolizumab-chemotherapy combinations in unselected patients with non-squamous advanced NSCLC compared with chemotherapy alone (platinum plus pemetrexed) (42). These results were confirmed by the Phase 3 KEYNOTE 189 trial (43) in all PD-L1 subsets, even PD-L1-negative tumors (44). Pembrolizumab is therefore approved in combination with platinum and pemetrexed as the first-line therapy for non-squamous NSCLC in both the EU (45) and the US (46). Pembrolizumab monotherapy is also approved as the first-line therapy to treat patients with TPS ≥1% NSCLC in the US, and to treat patients with NSCLC TPS ≥50% in the EU.

2.2.3.2 Second- or third-line treatment options for patients who have progressed on or after PD1/PD-L1-based therapy

According to the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) clinical practice guidelines (47, 48), following disease progression after PD1/PD-L1-based therapy (which may include chemotherapy) as 1L or 2L therapy, patients without driver gene mutations may receive a variety of combinations of cytotoxic chemotherapies, pemetrexed (for non-squamous histology), docetaxel, or docetaxel plus ramucirumab as second- or third-line therapy depending on prior chemotherapies received, contraindications and patients' decision. Clinical studies may be offered to patients who are ineligible or decline further chemotherapy.

Despite the progress made in the clinical management of advanced NSCLC with PD1/PD-L1-based therapies, prognosis of the disease has not improved substantially. Early success with PD1 axis inhibitors has improved 5-year long-term survival rates from 9%-13% to approximately 15%-23% of patients with advanced NSCLC (49, 50, 51, 52, 53, 54). The treatment of NSCLC remains a highly unmet medical need.

2.2.3.3 Nab-Paclitaxel as second-line therapy

Despite the availability of second- or third-line therapy, the trend of increased use of pemetrexed in 1L and maintenance settings potentially limits the available second- or third-line treatment options for many patients. Furthermore, not all patients are able to tolerate docetaxel or combination chemotherapies. Nab-Paclitaxel exhibits a 10-fold mean increase of the C_{max} of free paclitaxel and delivers a 33% higher drug concentration to tumors in preclinical xenograft models (55, 56). When administered (without steroid premedication) with carboplatin in the first-line setting, weekly nab-paclitaxel has demonstrated a more favorable efficacy and safety profile compared to Q3W schedule. Recently published data have demonstrated efficacy of nab-paclitaxel as monotherapy in the second-line setting in advanced non-squamous NSCLC with 16.3% response rate (57). One of the regimens this study will assess is weekly nab-paclitaxel, administered on Days 1 and 8 of each 21-day cycle. The allowance of a one-week rest period in this study (ie, no treatment on Day 15), takes into account research findings from other taxanes, whereby patients in the second-line setting are unlikely to tolerate the same dose-intensity compared to chemo-naïve patients (eg, sharper dose reduction in the second-line setting).

2.2.3.4 Interleukin-2 as a treatment option for NSCLC

In contrast to agents that block immune checkpoints, IL-2-based cytokine treatments target the IL-2Rβγ pathway, thereby augmenting lymphocyte responses. For more than 20 years, single-agent IL-2 (aldesleukin) treatment has shown efficacy in metastatic melanoma and RCC, but there have been only anecdotal reports of efficacy in other cancers including NSCLC. Moreover, effective aldesleukin treatment requires doses that invariably generate substantial toxicity, necessitating inpatient administration and intensive supportive care, restricting its widespread use (58).

Bempegaldesleukin (NKTR-214) is an investigational engineered IL-2 cytokine prodrug that provides sustained activation of the IL-2 pathway with a bias to IL-2Rβ. It has been shown to increase TILs, T-cell clonality, and PD-L1 expression (59, 60). The safety and clinical activity of bempegaldesleukin plus the immune checkpoint inhibitor (ICI) nivolumab were evaluated in PIVOT-02, a multicenter Phase 1/2 study in various advanced solid tumors (61, 62, 63, 64, 65). The combination was tolerable and showed encouraging clinical activity, regardless of baseline PD-L1 status (64) with durable responses that deepened over time (65). Bempegaldesleukin plus nivolumab was shown to convert baseline tumors from PD-L1(-) to PD-L1(+) (61, 62, 63, 64) which was associated with clinical benefit (61). Based on these data, bempegaldesleukin plus nivolumab received Breakthrough Therapy Designation from the US Food and Drug Administration for patients with previously untreated, unresectable or metastatic melanoma. Two multiple-cohort early phase clinical studies assessing efficacy of bempegaldesleukin with ICI monotherapy, ICI-CTLA4 combination, or ICI-chemotherapy combination in NSCLC in addition to other solid tumors, are currently enrolling globally (PIVOT-02 NCT02983045 and PROPEL NCT03138889). Preliminary data from PIVOT-02 showed that 3 out of 6 NSCLC patients responded to BEMPEG with nivolumab as 1 L or 2 L therapy. Five out of 6 NSCLC patients had known PD-L1 status and all were negative. All 3 responders were PD-L1 negative (61).

2.2.3.5 Rationale for combining SAR444245 with pembrolizumab or with pembrolizumab plus chemotherapy

SAR444245 is a non-alpha IL-2 that 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. Combining SAR444245 with either pembrolizumab or pembrolizumab plus chemotherapy may increase the anti-tumor immune response through the complementary immune modulatory effects of pembrolizumab, chemotherapy and SAR444245. In vitro studies demonstrated that SAR444245 in the presence of an anti-PD1 antibody increased T cell receptor (TCR) dependent IFN-γ secretion (Synthorx Report No. NCLN-707-010 Evaluation of Antigen Presenting Cell-mediated T Cell Activation by THOR-707 and in Combination with Nivolumab Employing an Allogeneic Human Mixed Lymphocyte Reaction (MLR) Assay System). These findings suggest that in the tumor microenvironment (TME) and draining lymph nodes, this combination treatment can potentially facilitate TCR-driven activation of lymphocytes to activate both effector memory (in the tumor) and naïve (in the draining lymph node) CD8+ T cells and exert cytolytic activity. This hypothesis is further supported by in vivo studies in a mouse CT-26 colon cancer model of anti-tumor activity of SAR444245 as monotherapy and in

combination with an anti-PD1 antibody. Notably, the combination treatment of anti-PD1 and SAR444245 prolonged survival compared to each monotherapy (Synthorx Report No. NCLN-707-007. Efficacy of THOR-707 as a single agent and in combination with an anti-PD1 antibody in CT-26 colon tumor-bearing Balb/c mice).

Accumulating evidence suggests that immune activation plays an important role in the efficacy of chemotherapy (66). The immunological effects of chemotherapy are complex and can be influenced by many different factors, but generally chemotherapy is thought to modulate the TME through the release of tumor antigens, activation of antigen presenting cells and depletion of immunosuppressive regulatory T and myeloid cells (67, 68, 69, 70, 71, 72, 73). The addition of an immunotherapy to platinum chemotherapy was assessed in KEYNOTE-189 (43) and KEYNOTE-407 (74) which successfully demonstrated prolonged overall survival with the combination of pembrolizumab and chemotherapy vs chemotherapy for patients with non-squamous NSCLC and squamous NSCLC, respectively. These studies established the therapeutic potential of combining an immunotherapy (anti-PD1) with platinum- or taxane-based chemotherapies.

Therefore, this Phase 2 study will further assess the potential synergistic activity of SAR444245 with pembrolizumab or pembrolizumab plus chemotherapy in first-line and second/third-line treatment in different cohorts of participants with advanced NSCLC, from an antitumor activity and safety standpoint. Cohort B1 and Cohort B2 will enroll patients who progressed on prior ICI therapy (eg, as their first-line or second-line therapy) as it is hypothesized that the combination of SAR444245, or SAR444245 plus nab-paclitaxel may re-sensitize the disease to allow the patient to respond.

2.2.4 Rationale for malignant pleural mesothelioma and selected participant population (Cohort C1)

Previously considered to be rare, malignant pleural mesothelioma (MPM) is a highly aggressive tumor that has become a very important issue over recent years. Asbestos exposure is the main factor involved in pathogenesis, which can explain the rise in incidence of MPM since the 1970s (75, 76). A combination of cisplatin (or carboplatin if necessary) and pemetrexed is currently the standard of treatment as first-line chemotherapy for patients with MPM (77, 78). No chemotherapy can be recommended as second-line after failure of chemotherapy including cisplatin, except pemetrexed if the patient did not have tumor progression at least 3 to 6 months after the end of pemetrexed-based first-line chemotherapy (77, 78). However, ultimately all patients experience disease progression. Therapeutic options in second or third-line are limited, and currently there is no standard recommended therapy in such setting (77, 78, 79).

2.2.4.1 PD1/PD-L1 inhibitors as treatment options

Malignant pleural mesothelioma is characterized by multiple histology patterns, and molecular/immunophenotypes. Using a 1% tumor cell positivity threshold, PD-L1 expression has been recognized in 14% to 72.4% of MPMs and reveals consistent association with non-epithelioid histology (eg, sarcomatoid/biphasic) and elevated TILs (80, 81, 82, 83, 84, 85, 86). Cases with PD-L1 expression revealed a higher fraction of Tregs and effector T cells positive for immune inhibitory receptors (87).

Promising activity has been observed with different agents targeting the PD-L1 axis when administered as a single agent after first-line CT failure (88, 89, 90, 91, 92, 93). Nevertheless, these encouraging results have not been confirmed in a recent Phase 3 trial, comparing pembrolizumab with second-line standard chemotherapy, which failed to reveal any survival differences between the two treatment arms (94). Combining ICI with anti-CTLA-4 emerged as an effective and tolerable strategy in the salvage setting, as documented in the MAPS2 trial with one-third of patients receiving nivolumab plus ipilimumab alive at 2 years (92).

2.2.4.2 Interleukin-2 as a treatment option for MPM (Cohort C1)

Many studies have evaluated cytokine therapy in the treatment of MPM. Intravenous, subcutaneous and intrapleural administrations of IL-2 have shown some effects on tumor regression in MPM and were tolerable. Intrapleural administration of IL-2 in patients with earlier stage generally resulted in 15% to 25% response (95, 96, 97). However IV and subcutaneous administration of IL-2 from a Phase 2 study showed only limited activity (98).

2.2.4.3 Rationale for combining SAR444245 with pembrolizumab

The antitumor activity observed in in vitro studies and in vivo mouse studies of SAR444245 in the presence of an anti-PD1 antibody is described in Section 2.2.3.5.

2.3 BENEFIT/RISK ASSESSMENT

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

2.3.1 Risk assessment

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

Risk assessment of SAR444245 combined with pembrolizumab results therefore from anticipated risks for SAR444245 and from the label information for pembrolizumab, taking into account potential overlapping risks.

Table 23 summarizes potential risks for SAR444245 identified from preclinical experience and from the Phase 1/2 first-in-human (HAMMER) study, as well as available safety data for pembrolizumab, along with proposed mitigation strategies.

2.3.1.1 Aldesleukin experience

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

Aldesleukin is a human recombinant interleukin-2 which has been shown to possess the biological activities of human native IL-2 mediated through its binding with the high-affinity IL-2Rαβγ and intermediate-affinity IL-2Rβγ receptors. The widespread use of aldesleukin has been limited by its low response rate, a short $t_{1/2}$ that requires dosing three times per day, and toxicities (99), 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 (100). 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 (101). As SAR444245 also exercises IL-2 activity, the Investigator should monitor clinical effects of narrow therapeutic index drugs that are hepatically metabolized.

Please refer to Proleukin Label and Summary of Product Characteristics (SmPC) for more detailed information.

2.3.1.2 SAR444245

2.3.1.2.1 Preclinical data

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

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

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

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

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

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

No data pertaining to pregnancy and lactation exposure and outcomes are available for SAR444245. Due to the missing information for this important risk, detailed mitigation measures will be introduced. Conditions for eligibility of women of reproductive potential and male subjects with female partners of childbearing potential are detailed in Section 5.1. Also, since 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 (60).

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 NSCLC). Several treatment regimens were explored. The dose of 0.009 mg/kg had excessive toxicity (2 of 3 patients with DLT: Gr 3 hypotension [n=1] & Gr 4 hyperglycemia + metabolic acidosis [n=1]) when combined with 360 mg of nivolumab. All 38 patients had TEAEs that were considered related to the study combination. The MTD of the combination was defined as NKTR-214 0.006 mg/kg + nivolumab 360 mg 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 significantly reduced thereafter. There were no

treatment-related deaths and generally, Grade ≥3 TRAEs were manageable using standard guidelines. Tumor responses were observed regardless of baseline PD-L1 status and baseline levels of tumor-infiltrating lymphocytes, suggesting therapeutic potential for patients with poor prognostic risk factors for response to PD1/PD-L1 blockade. These data demonstrated that NKTR-214 can be safely combined with a checkpoint inhibitor as dual immunotherapy for the treatment of a range of advanced solid tumors (102).

2.3.1.4 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.

The use of pembrolizumab is commonly associated with infusion-related reactions (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and CRS), 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 risk for pembrolizumab (45).

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 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, USPI, SmPC) for pembrolizumab for more detailed information.

2.3.1.5 SAR444245 combined with pembrolizumab and SAR444245 combined with pembrolizumab and chemotherapy regimen

SAR444245 combined with pembrolizumab

Due to synergistic action of SAR444245 and pembrolizumab, combining these two substances may lead to an increased frequency and/or severity of AEs related to immune 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 2.3.1.4).

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

SAR444245 combined with pembrolizumab and chemotherapy regimen

Safety data from KEYNOTE-189 (pembrolizumab + pemetrexed and platinum) (43), KEYNOTE-407 (pembrolizumab + carboplatin and paclitaxel or nab-paclitaxel) (74) with non-squamous NSCLC and squamous NSCLC, respectively, clearly demonstrated that combinations of standard dosing of pembrolizumab with chemotherapy are achievable with a manageable toxicity profile. Updated analysis of KEYNOTE-189 safety and tolerability results after a median follow-up of approximately 2 years continue to show results comparable with the first interim analysis of 10.5 months medium follow-up (44).The most common adverse events in the pembrolizumab combination group versus placebo group were nausea (56.8% versus 53.0%), anemia (47.4% versus 48.5%) and fatigue (42.5% versus 38.6%). The most common immune-mediated adverse events in the pembrolizumab combination group were hypothyroidism (7.9%), hyperthyroidism (4.9%), pneumonitis (4.9%), colitis (3%) and infusion reactions (2.7%).

The combination of SAR444245, pembrolizumab and chemotherapy (pemetrexed, platinum, nab-paclitaxel) are expected to have overlapping toxicities based on each drug's toxicity profile.

2.3.2 Benefit assessment

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

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

Both NSCLC and mesothelioma are tumor types that are benefiting from ICI treatment. The companion ICI (anti-PD1) pembrolizumab to be combined with SAR444245 in this study is approved to treat various disease settings of NSCLC, and few other anti-PD1/PD-L1 (for example, nivolumab and atezolizumab) are approved for the treatment of similar disease settings of NSCLC. For pleural mesothelioma, nivolumab is accelerated approved in Japan for this tumor type. In April 2020, interim analysis of Phase 3 confirmatory trial in patients with unresectable pleural mesothelioma met the primary end point of the OS (CheckMate-743).

In a syngeneic mouse model CT-26, relatively resistant to immune checkpoint treatment, SAR444245 potentiated the activity of an anti-PD1 antibody. Combination treatment in animals, when compared to respective monotherapies, increased the number of complete responses and prolonged survival which was durable as demonstrated by the failure of the tumor to grow upon re-engraftment on the tumor free animals, indicating the establishment of durable memory T-cell population in response to the initial treatment (see SAR444245 IB). Furthermore, preliminary clinical data from another new generation IL-2, NKTR-214, induced an increase in ORR and better quality of response than historical data for anti-PD1 treatment alone in ICI-naïve NSCLC patients (41). Two out of 5 treated patients achieved CR, and 1 patient achieved PR. Among the 5 patients, 3 were PD-L1 negative (<1%) and 2 were PD-L1 positive (>1%).

The combination regimens of SAR444245 plus pembrolizumab and SAR444245 plus pembrolizumab plus chemotherapy (pemetrexed, platinum, nab-paclitaxel), proposed to be evaluated in this study, are anticipated to benefit participants in the ICI-naïve NSCLC and mesothelioma cohorts. For the ICI-treated NSCLC cohorts, clinical benefit may be observed based on preclinical data.

2.3.3 Overall benefit: risk conclusion

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

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with this new generation IL-2 SAR444245 combined with the anti-PD1 inhibitor pembrolizumab and other anticancer treatments are justified by the anticipated benefits that may be afforded to participants with NSCLC or pleural mesothelioma.

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

Participants potentially eligible for this study have advanced or metastatic NSCLC or mesothelioma. Patients with lung cancer may be particularly vulnerable to complications from COVID-19. In an initial retrospective analysis of COVID-19 outcomes among 105 patients with cancer in Wuhan, People's Republic of China, patients with lung cancer had the second highest rates of mortality from COVID-19, behind only those with hematologic malignancies (103). More recent studies have confirmed the high rates of hospitalization and death within thoracic oncology populations affected by COVID-19. For example, in the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry (104), which pooled data from 200 patients with lung cancer (including 8 patients with mesothelioma) across 42 institutions and eight countries, 76% of the patients of thoracic oncology with COVID-19 required hospitalization and 33% died. Importantly, recent data from Luo et al. (105, 106) suggest that patient-specific factors, such as smoking status and chronic obstructive pulmonary disease, rather than disease-specific factors (eg, previous surgery, systemic therapy) are the major determinants of COVID-19 infection severity among patients with lung cancer.

There are no evidence-based guidelines for the management of lung cancer in the era of COVID-19. However, several guidelines designed to help make clinical decisions have been published. These include the ESMO Guidelines (107), and the National Comprehensive Cancer Network recommendation (108). ESMO Guidelines indicate that, in order to limit cancer-related mortality in patients with a new diagnosis of metastatic NSCLC, all standard options for first-line systemic therapy should be envisaged unaltered, including chemotherapy and immunotherapy. Discontinuation of ICIs after 2 years should be discussed.

Testing for severe acute respiratory syndrome coronavirus 2 (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, dose modification of study intervention should be based on the recommendations provided in Section 6.6. In addition, all Investigators are instructed to consult official COVID-19 clinical research guidance from their local hospital/institution along with other relevant resources, such as the American Society of Clinical Oncology (ASCO) (109) or ESMO (110).

2.3.4.1.2 Risks related to study treatment

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

The impact of PD-1 blockade therapy on COVID-19 severity is also explored by 2 groups and did not find a clinically meaningful signal (111, 105).

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 10.11, 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 NSCLC and mesothelioma during the COVID-19 pandemic. The Sponsor will continue to evaluate benefit-risk during the study period.

3 OBJECTIVES AND ENDPOINTS

Table 3 - 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 CR or partial response (PR), determined by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (1) for Cohort A1, Cohort A2, Cohort A3, Cohort B1 and Cohort B2; per modified RECIST (mRECIST) (2) for Cohort C1.
Secondary	
• To confirm the dose and to assess the safety profile of SAR444245 when combined with other anticancer therapies.	• Incidence of TEAEs, DLTs, SAEs, laboratory abnormalities according to NCI CTCAE V5.0 and ASTCT consensus gradings (3).
• To assess other indicators of antitumor activity.	• Time to response defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma). • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until progressive disease (PD) determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma) or death from any cause, whichever occurs first. • Clinical benefit rate (CBR) including CR or PR at any time plus stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1 [for NSCLC] or mRECIST [for mesothelioma]). • 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 for NSCLC) or mRECIST (for mesothelioma) or death due to any cause, whichever occurs first.
• To assess the plasma concentrations of SAR444245 when given in combination with pembrolizumab.	• Plasma concentrations of SAR444245.
• To assess the immunogenicity of SAR444245.	• Incidence of anti-drug antibodies (ADAs) against SAR444245.

Objectives	Endpoints
Exploratory	
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

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

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

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245-based therapies in participants with NSCLC or mesothelioma.

Cohort A1, Cohort A2 and **Cohort A3** will assess the antitumor efficacy and safety of SAR444245 adding on to therapeutic approaches with documented efficacy profile as 1L NSCLC therapy. Participants with previously untreated Stage IV NSCLC will be enrolled sequentially based on histology and PD-L1 tumor proportion score (TPS**)** to Cohort A1, Cohort A2 and Cohort A3.

- **Cohort A1**: participants with PD-L1 TPS ≥50% NSCLC, to receive SAR444245 + pembrolizumab as 1L therapy.
- **Cohort A2**: participants with PD-L1 TPS 1%-49% NSCLC, to receive SAR444245 + pembrolizumab as 1L therapy.
- **Cohort A3**: participants with non-squamous NSCLC, to receive SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin as 1L therapy.

Cohort B1 and **Cohort B2** will assess SAR444245-based therapies as 2/3L NSCLC therapy when receiving SOC is not in the best interest of participants or where no SOC is established.

- **Cohort B1**: participants with NSCLC, to receive SAR444245 + pembrolizumab as 2/3L therapy.
- **Cohort B2:** participants with NSCLC, to receive SAR444245 + pembrolizumab + nab-paclitaxel as 2/3L therapy.

Cohort C1 will evaluate SAR444245-based therapy as 2/3L mesothelioma treatment where no SOC is well established. Participants with mesothelioma who have experienced disease progression during or after at least 1 but no more than 2 prior regimens (detailed in Section 5.1 Inclusion Criteria I 06) will be enrolled

- **Cohort C1**: participants with mesothelioma, to receive SAR444245 + pembrolizumab as 2/3L therapy.

The study consists of a safety run-in and a core phase for all 6 cohorts and an expansion phase for Cohorts B1 and/or B2. In the core phase approximately 40 participants will be treated at confirmed safe dose per cohort. The results of an interim analysis will decide if the expansion phase will be opened for Cohorts B1 and/or B2. Approximately 57 additional participants are planned to be enrolled in each of these cohorts for the expansion phase in order to better assess antitumor activity. A graphical presentation of the study is shown in Figure 1. An overview of the study intervention and disease being treated for each cohort is provided in Table 4.

Table 4 - Overview of cohorts

Cohort	Study intervention	Disease	Primary tumor assessment criteria
A1	SAR444245 + pembrolizumab as 1L therapy	NSCLC, PD-L1 TPS ≥50%	RECIST 1.1
A2	SAR444245 + pembrolizumab as 1L therapy	NSCLC, PD-L1 TPS 1%-49%	RECIST 1.1
A3	SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin as 1L therapy	non-squamous NSCLC	RECIST 1.1
B1	SAR444245 + pembrolizumab as 2/3L therapy	NSCLC	RECIST 1.1
B2	SAR444245 + pembrolizumab + nab-paclitaxel as 2/3L therapy	NSCLC	RECIST 1.1
C1	SAR444245 + pembrolizumab as 2/3L therapy	mesothelioma	mRECIST

1L = First-line; 2/3L = Second- or third-line; mRECIST = Modified response evaluation criteria in solid tumors; NSCLC = Non-small cell lung cancer; PD-L1 = Programmed cell death-ligand 1; RECIST = Response evaluation criteria in solid tumors; TPS = Tumor proportion score.

A safety run-in will confirm the dose of SAR444245 in each regimen tested in this study, namely: **SAR444245 + pembrolizumab; SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin; SAR444245 + pembrolizumab + nab-paclitaxel**. Participants who fulfill the eligibility criteria of any cohorts testing the regimen may be enrolled to the safety run-in of that regimen. Participants will be enrolled across Cohorts A1, A2, B1 and C1 to receive SAR444245 and pembrolizumab. Enrollment will be paused once at least 6 participants are evaluable for DLT. Safety data for these participants will be reviewed by a Study Board (SB), comprising Investigators or designees participating in the safety run-in part of applicable cohorts and the Sponsor clinical team members. DLT-evaluable participants include all treated participants in the safety run-in who have been observed for at least 21 days. Any participant who experienced a DLT during the first 21 days will also be DLT-evaluable. If no safety concerns are identified by the SB, participant enrollment will continue for the 4 cohorts. If after recruiting the first 10 participants there are fewer than 6 participants evaluable for DLT, more participants will be enrolled to ensure at least 6 DLT evaluable participants after agreement from SB. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants in the core phase for that specific cohort (for example, if 3 Cohort A1 participants are enrolled in the safety run-in and treated at the confirmed safe dose, approximately 37 additional participants will be enrolled into Cohort A1 to have the total number of 40 participants).

The safety run-in for other regimens **ie, SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin; and SAR444245 + pembrolizumab + nab-paclitaxel** will not be opened until SAR444245 + pembrolizumab dose is confirmed, and enrollment of Cohort A2 and Cohort B1, respectively, is stopped. Details of the opening sequence of the different cohorts are described below.

The SAR444245 dose to be confirmed is 24 µg/kg, administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle). Overall safety monitoring will be performed throughout the study. If recommended by the SB, SAR444245 dose level may

be reduced to [redacted] or another lower dose level which will be explored following the same process described in the safety run-in for 24 µg/kg dose level.

The DLT observation period is 21 days and will take into account the occurrence of DLT. The Modified Toxicity Probability Interval 2 (mTPI2) design will be used in the safety run-in part. The mTPI2 design is a Bayesian interval design that can be implemented in a simple fashion as the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics. The target toxicity rate for the MTD is 0.3, with the acceptable toxicity probability interval of (0.25,0.35). The dose decision (stay at 24 µg/kg dose or reduce the dose) will be made by the SB and will be guided by the decision rules from the mTPI2 design. The mTPI2 decision rules are based on calculating the unit probability mass (UPM) of intervals as follows: (0, 0.05), (0.05, 0.15), (0.15, 0.25), (0.25, 0.35), (0.35, 0.45) …… (0.85, 0.95), (0.95, 1). In the mTPI2 method, intervals that are lower than 0.25 indicate dose escalation, equivalence interval (0.25,0.35) indicates staying at the current dose level, and intervals that are higher than 0.35 indicate dose de-escalation. The interval with the largest UPM is the winning interval and implies the corresponding dose escalation/de-escalation decision. For the safety run-in part of the study, mTPI2 rules (see Table 5) will be applied as follows, unless decided otherwise by the SB:

- If the dose recommendation from mTPI2 is "E" (Escalate to the next higher dose) or "S" (Stay at the same dose), all cohorts treated at the current regimen will continue with the SAR444245 24 µg/kg dose;
- If the dose recommendation from mTPI2 is to de-escalate to a lower dose (either "D" [De-escalate to the previous lower dose] or "DU" [De-escalate to the previous lower dose and the current dose will never be used again in the trial]), a dose lower than 24 µg/kg will be tested and assessed with the same methodology.

Table 5 - Dose escalation rule of the modified toxicity probability interval-2 method

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

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

Dose limiting toxicity: The following events occurring during the DLT observation period (21 days of first cycle) are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245. Based on the occurrence of DLT and overall assessment of safety data supplemented with data from other SAR444245 studies, the SB will determine if the dose of SAR444245 needs to be reduced to [redacted] or another lower dose level, in agreement with the Sponsor.

Hematologic abnormalities:

- Grade 4 neutropenia for ≥7 consecutive days.
- Grade 3 or 4 neutropenia complicated by fever (temperature of >38.3°C [101°F] or a sustained temperature of ≥38.0°C [100.4°F] for more than 1 hour) or microbiologically or radiographically documented infection.
- Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention.

Non-hematologic abnormalities:

- Grade 3 or above alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with a bilirubin >2 times upper limit of normal (ULN) with no evidence of cholestasis or another cause such as viral infection or other drugs.
- Grade 3 or above Vascular Leak Syndrome (VLS).
- Grade 3 or above hypotension.
- Grade 3 or above cytokine release syndrome.
- Other Grade 3 or above AE except:
  - Grade 3 fatigue that resolves within 1 week.
  - Grade 3 nausea, vomiting, or diarrhea that resolves within 72 hours with antiemetics and standard supportive care measures.
- Any Grade 3 non-hematologic laboratory value

  Exceptions:
  - Grade 3 electrolyte abnormalities that are not clinically complicated and resolve within 72 hours with conventional medical interventions.
  - Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
- Any Grade 4 non-hematologic laboratory value.

Other abnormalities:

- Any death not clearly due to the underlying disease or extraneous causes.
- Any toxicity requiring permanent discontinuation of the study drug(s).

Study Board

The study Investigators (or designee) participating in the safety run-in of applicable cohorts and the Sponsor clinical team members will constitute the Study Board (SB). The SB will review clinical data on a regular basis in order to decide dose confirmation or dose reduction on the basis of their knowledge of the safety data. Minutes of each meeting will be written by the Sponsor and distributed to all sites participating in the safety run-in. Decisions regarding final dose selection will be made during one of the SB meetings and documented in the meeting minutes. After safety run-in dose confirmation, occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants per regimen will trigger SB to rapidly convene to assess safety, or need to pause enrollment to allow for a safety review. The SB (during safety run-in), IDMC (during core phase and expansion) and Sponsor can decide to stop any cohort in the event excessive toxicity (for example but not limited to excessive irAE or excessive number of G4/5 events) is observed.

Safety run-in and core phase enrollment sequence

SAR444245 and pembrolizumab - Cohorts A1, A2, B1 and C1

As safety run-in of this regimen is opened first, Cohorts A1, A2, B1 and C1 will be the initial cohorts to enroll.

A safety run-in will also be performed for Cohorts A3 and B2 in the sequence described below.

SAR444245, pembrolizumab, pemetrexed, and carboplatin/cisplatin - Cohort A3

Once enrollment is completed for Cohort A2, the safety run-in of Cohort A3 can be conducted with up to 10 participants enrolled to receive SAR444245, pembrolizumab, pemetrexed, and carboplatin/cisplatin prior to an enrollment pause. If Cohort A1 is still enrolling when Cohort A3 is opened, a participant who is eligible for both Cohorts A1 and A3 should be enrolled in Cohort A1 until Cohort A1 enrollment is completed.

Participants who are enrolled into Cohort A3 and the safety run-in of Cohort A3 and treated at the confirmed safe dose will be included in the total number of participants for Cohort A3.

SAR444245, pembrolizumab, and nab-paclitaxel - Cohort B2

Once enrollment is completed for Cohort B1, the safety run-in of Cohort B2 can be conducted with up to 10 participants enrolled to receive SAR444245, pembrolizumab, and nab-paclitaxel prior to an enrollment pause. Participants who are enrolled into Cohort B2 in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants for Cohort B2.

Additional cohorts with different regimens or indications may be added to this protocol.

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

The duration of the study for a participant will include:

- **Screening period**: up to 28 days.
- **Treatment Period**: enrolled participants will receive continuous treatment until PD, unacceptable AE, other full permanent discontinuation criteria as described in Section 7, or completion of Cycle 35 (for Cohorts A1, A2, B1, B2 and C1).
- **End of Treatment and Follow-up.** End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **EOT**:
  1. Participants who discontinue study treatment **without radiological or clinical PD** or who **complete 35 cycles of treatment without PD** (per RECIST 1.1 or mRECIST), will be followed every 3 months ±7 days from last IMP administration, for safety (as per Section 1.3) 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 radiological or clinical PD** (per RECIST 1.1 or mRECIST) **or** [redacted] will be followed in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration before moving to the **Survival Phone Call Follow-Up Period**.

Participants who move into the **Survival Phone Call Follow-Up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, and best reported response, and date of progression will also be collected. Survival Phone Call Follow up will continue until death, participant request to discontinue from follow-up, or final cohort cut-off, or upon cancellation of Survival Follow up at the discretion of the Sponsor at any prior timepoint.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that combining the ICI pembrolizumab with the non-alpha IL-2 SAR444245 with or without chemotherapy will result in a significant increase in the population experiencing an objective response rate.

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, chemo-immune combination, or available chemotherapy as a benchmark to show outstanding objective response rate. The ORR will be assessed using RECIST 1.1 for participants with NSCLC, and modified RECIST for participants with mesothelioma. The objective response will be assessed per Investigator in first intention. Central imaging reading may be done retrospectively if significant activity is observed.

A safety run-in on the first 6-10 participants being enrolled to each regimen has been embedded in the study to confirm the absence of safety issue before launching enrollment of the remaining participants. Some NSCLC cohorts may be expanded to enroll more participants to accumulate evidence of clinical activity.

4.2.1 Participant input into design

There was no participant input into the design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 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.

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

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

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 in the cohort of patients receiving SAR444245 24 µg/kg Q3W in combination with cetuximab.

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 AE in the 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) and gamma-glutamyl transferase (GGT) increased (2 participants each for AST and ALT increased, 33.3%; 1 participant for GGT increased, 16.7%), Grade 3 blood phosphorus decreased and 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) were Grade 3 chills (1 participant, 20.0%) and Grade 3 abdominal pain, vomiting and pyrexia (each in 1 participant, 20.0%).

Within the HAMMER study, a total of 13 patients experienced a CRS event of any grade (per CTCAE version 5) as of 18 June 2021. 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%) was reported among participants who received SAR444245 monotherapy (n=38). Among participants who received SAR444245 in combination with pembrolizumab (n=20), grade 3 CRS (with 16 µg/kg Q3W) was 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 patients who experienced CRS in the HAMMER Phase 1 study did not always receive peri-infusion hydration. Based on this learning, hydration and CRS management guidelines are included in this study.

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.

Unlike 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 has less impact on immunosuppressive Treg cells. Therefore, the PDy change of CD8+ T, NK and Treg cells is closely monitored in HAMMER study as supportive information for RP2D 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 postdose was 1.75-fold. For dose levels 16 µg/kg and 24 µg/kg, the peripheral blood CD8+ T cell expansion was 2.47- and 4.47-fold at the day 8 postdose peak of expansion. The day 8 sample timepoint was added after the first 3 participants in the 8 µg/kg cohort were dosed.

In addition, the average increase in peripheral blood NK cells was 4.22-fold at 72 hours for 8 µg/kg. The 16 µg/kg and 24 µg/kg dose levels resulted in 5.9- and 7.67-fold NK expansion, compared to baseline at the Day 8 peak expansion.

Among the dose levels tested to date for SAR444245 in combination with pembrolizumab administered using Q3W schedule, PDy data are available 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 Day 8 peak expansion. Moreover, 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). This study showed that SAR444245-induced cytokine release in human whole blood was not affected in the presence of pembrolizumab at Q3W schedule (please refer to the SAR444245 IB for details).

This study proposes to evaluate the clinical benefit of SAR444245 24 µg/kg combined with pembrolizumab 200 mg (see Section 4.3.2), using a Q3W schedule of administration, with initial dose confirmation in a cohort of approximately 6-10 patients considering that:

- SAR444245 monotherapy up to 32 µg/kg Q3W, pembrolizumab combination up to 32 µg/kg Q3W and cetuximab combination 24 µg/kg Q3W were all cleared in the HAMMER study;
- sustained relevant PDy effect in blood, higher at higher doses, was documented in participants;
- observed safety data from the Hammer study suggests the combination of SAR444245 combined with anti-PD1 (eg, pembrolizumab) may not lead to significant overlapping toxicities.

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 and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W).
- 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

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. For participants enrolled in France and Japan please refer to Section 10.7.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply for a given cohort:

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. Cancer diagnosis at study entry:

- *For participants in Cohorts A1, A2, B1 and B2* - Histologically or cytologically confirmed diagnosis of Stage IV (per American Joint Committee on Cancer [AJCC] 8th edition [112]) NSCLC,
- *For participants in Cohort A3* - Histologically or cytologically confirmed diagnosis of Stage IV (per AJCC 8th edition) non-squamous NSCLC,
- *For participants in Cohort C1* - Histologically confirmed unresectable MPM.

I 03. PD-L1 expression TPS as determined (with an absolute value provided to Sponsor) at local laboratory (for details on PD-L1 assay, please refer to lab manual).

- *For participants in Cohort A1* - PD-L1 expression TPS ≥50%,
- *For participants in Cohort A2* - PD-L1 expression TPS 1%-49%.

I 04. Provision of tumor tissue:

- **Mandatory** baseline biopsy for participants to **Cohorts A1 and A2 in Core Phase** (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)** AND **all cohorts for Expansion Phase (**minimum **10 slides with 4-5 micron thickness)**. 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. Slide specifications are detailed in Lab Manual.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - Location of the tumor not amenable to biopsy due to significant risk, OR,

- Less than required number of slides or archival tumor tissue sample collected more than 6 months prior to first IMP administration.

- **Optional per Investigator's discretion and evaluation** for participants to **Cohorts A3, B1, B2 and C1 in Core Phase**.

I 05. Measurable disease:

- *For participants in Cohorts A1, A2, A3, B1 and B2* - 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.
- *For participants in Cohort C1* - At least 1 measurable lesion per modified RECIST criteria for mesothelioma (either a pleural lesion with tumor thickness perpendicular to the chest wall or mediastinum measurable on transverse cuts of CT scan, or non-pleural lesion >1 cm - for details, see Section 10.10) (2). Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site.

I 06. Prior anticancer therapy

- *For participants in Cohorts A1, A2 and A3* - Have not received prior systemic therapy for advanced/metastatic NSCLC. Participants who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the development of metastatic disease.
- *For participants in Cohorts B1 and B2*:
  - Patients with metastatic NSCLC should have progressed after having received prior benefit from an anti-PD1/PD-L1* containing regimen (SD, partial response [PR], or CR). Patients must have received prior anti-PD1/PD-L1 containing regimen given concurrently or sequentially with a platinum-based chemotherapy. Patients who received concurrent anti-PD1/PD-L1 chemotherapy combination are allowed to receive one additional chemotherapy. Platinum ineligible patients can enroll after anti-PD1/PD-L1 monotherapy, or anti-PD1/PD-L1 monotherapy followed by a non-platinum form of chemotherapy.

    *If anti-PD1/PD-L1 was used beyond initial radiological progression while continuing to use the same anti-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.
- *For participants in Cohort C1* - At least 1 but no more than 2 prior systemic treatments for advanced mesothelioma that included a pemetrexed-based regimen in combination with platinum agent. For participants in whom pemetrexed was contraindicated or not tolerated, prior therapy with a first-line platinum-based regimen is required.

I 07. *For participants in Cohorts B1 and B2* - Based on the Investigator's judgment, at this time, either docetaxel or pemetrexed is not the best treatment option for this specific participant. The eligibility of participant to take part in the study will be validated at the multidisciplinary collegial meeting in countries listed in Section 10.7 of the protocol. See wording specific to Japan in Section 10.7

Sex

I 08. All (male and female)

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

A) Male participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 330 days (for Cohort A3) or 210 days (for Cohorts A1, A2, B1, B2 and C1), [corresponding to time needed to eliminate study intervention(s) plus an additional 90 days (a spermatogenesis cycle)] after the last dose of study intervention:

- Refrain from donating or cryopreserving sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below
  - A male condom with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 (Section 10.4) of the protocol 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 (see wording specific to Japan in Section 10.7), 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 Appendix 4 (Section 10.4) during the intervention period (to be effective before starting the intervention) and for at least 420 days (for Cohort A3) or 150 days (for Cohorts A1, A2, B1, B2 and C1), [corresponding to the time needed to eliminate any study intervention(s) plus 30 days (a menstrual cycle)] after the last dose of study intervention.

- 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 and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4 (Section 10.4).
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 09. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol 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:

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 (Note: participants with brain involvement due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval from the Sponsor).
- Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) are eligible but will require regular imaging of the brain as a site of disease.

E 04. History of allogenic tissue/solid organ transplant (participants with prior corneal transplant may be allowed to enroll after discussion with and approval from Sponsor).

E 05. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD1/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 or local intervention within 28 days.

E 07. *For participants in Cohort A3* - Uncontrolled pleural/peritoneal effusion, pericardial effusion or ascites requiring recurrent drainage procedures (twice monthly or more frequently).

E 08. 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 09. 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 16), or other infection that is not controlled or requires IV or oral antibiotics.

E 10. 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 11. 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.

E 12. 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 13. Current pneumonitis or interstitial lung disease, or history of interstitial lung disease or pneumonitis that required oral or IV glucocorticoids to assist with management.

E 14. 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 15. Receipt of a live or live-attenuated virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 16. 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.

E 17. 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 hepatitis C virus (HCV) infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month prior to starting study intervention. Participants with positive HCV antibody and undetectable HCV RNA without anti-HCV therapy are eligible.

E 18. Known second malignancy either progressing or requiring active treatment within the last 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

E 19. *For participants in Cohort A3*. Participants with predominantly squamous cell histology NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible.

E 20. *For participants in Cohorts A1, A2, A3, B1, and B2* - Known driver alternations which include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Proto-oncogene tyrosine-protein kinase (ROS)1, or BRAF mutation for participants with non-squamous NSCLC.

E 21. Known hypersensitivity to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein.

E 22. Participants with baseline SpO_2 ≤92% (without oxygen therapy).

Prior/concomitant therapy

E 23. Has received prior IL-2-based anticancer treatment.

E 24. Is unable or unwilling to take premedication.

E 25. Deleted by protocol amendment 03

E 26. Participants treated under anti-hypertensive treatment who cannot temporarily (for at least 36 hours) withhold antihypertensive medications prior to each IMP dosing

E 27. *For participants in Cohorts A1, A2, A3, C1* - Prior treatment with an agent (approved or investigational) that blocks the PD1/PD-L1 pathway (participants who joined a study with an anti-PD1/PD-L1 but have written confirmation they were on control arm are allowed).

E 28. *For participants in Cohort A3* - Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

Prior/concurrent clinical study experience

E 29. Current enrollment or past participation in a study of an investigational treatment or has used 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 30. Absolute neutrophil count <1500 /μL (1.5×10^9/L) (after at least one week off G-CSF).

E 31. Platelets <100×10^3 μ/L (after at least 3 days without platelet transfusion).

E 32. 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 33. Total bilirubin >1.5 × 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 34. Aspartate aminotransferase and/or alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases).

E 35. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] Formula).

E 36. 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 37. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 38. Any country-related specific regulation that would prevent the participant from entering the study - see Section 10.7.

E 39. 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 40. 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 41. Any specific situation during study implementation/course that may raise ethics considerations.

E 42. History or current evidence of any condition, therapy that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

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

5.3.2 Caffeine, alcohol, and tobacco

No restrictions are required.

5.3.3 Activity

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

5.3.4 Hydration

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

5.4 SCREEN FAILURES

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

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

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

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

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol-mandated procedures, contingency measures are proposed in Section 10.11.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTIONS ADMINISTERED

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

6.1.1 Investigational medicinal product

Investigation medicinal product is defined as SAR444245, pembrolizumab, and chemotherapy administered in combination as described in Section 4.1. Details of each IMP component to be administered are shown in Table 6.

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

Hydration is required for SAR444245 and cisplatin infusions. Details are provided in Section 6.1.3.

Table 6 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab	Pemetrexed	Carboplatin	Cisplatin	Nab-paclitaxel
Type	Biologic	Biologic	Drug	Drug	Drug	Drug
Dose formulation	Concentrate for solution for infusion	Solution for infusion	Concentrate for solution for infusion (or any other formulation approved locally)	Concentrate for solution for infusion (or any other formulation approved locally)	Concentrate for solution for infusion (or any other formulation approved locally)	Powder for suspension for infusion (or any other formulation approved locally)
Unit dose strength(s)	2.0 mg/mL	25 mg/mL	As per locally approved formulation	As per locally approved formulation	As per locally approved formulation	As per locally approved formulation
Dosage level(s)[a]	24 µg/kg Q3W (or reduced to [redacted] or another lower dose level recommended by SB)	200 mg Q3W	500 mg/m^2 Q3W	AUC of 5 Q3W for 4 cycles	75 mg/m^2 Q3W for 4 cycles	100 mg/m^2, on Days 1 and 8 of each cycle for 6 cycles
Route of administration	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion

Intervention name	SAR444245	Pembrolizumab	Pemetrexed	Carboplatin	Cisplatin	Nab-paclitaxel
Use	Experimental	Treatment of cancer (combination)	Treatment of cancer (combination)	Treatment of cancer (combination)	Treatment of cancer (combination)	Experimental
IMP or NIMP	IMP	IMP	IMP	IMP	IMP	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.	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)	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)	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)	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)	NA	Keytruda	As per locally approved formulation	As per locally approved formulation	As per locally approved formulation	As per locally approved formulation

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

6.1.2 Non-investigational medicinal products

Non-investigational medicinal products (NIMP) include the premedication administered for SAR444245, pemetrexed, and cisplatin.

6.1.2.1 Premedication for SAR444245

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

- Acetaminophen (paracetamol) 650 to 1000 mg IV or PO, and then optionally thereafter as needed.
- Diphenhydramine 25 to 50 mg IV or PO (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter as needed.

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 the next cycle. If no IRR is observed for the next cycle without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during the next cycle without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent cycles.
- In case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, premedication no longer needs to be administered

6.1.2.2 Premedication for pemetrexed

All participants in Cohort A3 should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below:

- Folic acid 350-1000 µg oral: At least 5 daily doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg intramuscular injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1-4 but not to exceed doses in MASCC (Multinational Association for Supportive Care in Cancer) guidelines (5).

6.1.2.3 Premedication for cisplatin

All participants in Cohort A3 should receive premedication for cisplatin as per local practice and locally approved label.

6.1.3 Hydration guidelines for SAR444245 administration

[redacted]

6.1.4 Readiness for treatment of severe cytokine release syndrome

Doses of tocilizumab should be available at site at all times in the event that a participant requires rapid intervention for the treatment of severe CRS. Please refer to Section 6.6.5.3 for detailed guidelines for the management of CRS.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.9).

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 electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 CONCOMITANT THERAPY

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

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

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

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

6.5.1 Acceptable concomitant medications

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

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

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

Colony-Stimulating Factors

Routine use of colony-stimulating factors (CSFs) is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed (113). See requirements specific to Japan in Section 10.7.

Nonsteroidal Anti-Inflammatory Drugs

For Cohort A3, participants taking NSAIDs or salicylates will not take the NSAID or salicylate (other than an aspirin dose ≤1.3 g per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Participants taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

6.5.2 Prohibited concomitant medications

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

- Antineoplastic systemic chemotherapy 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 6.5.1 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 immune-mediated AEs when indicated (IRR, CRS, irAE, and ICANS see Table 12, Table 13, Table 14 and Table 16),
  - 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).
- Phenytoin during therapy with cisplatin/carboplatin.

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 Periods.

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

6.6 DOSE MODIFICATION

6.6.1 General rules

Dose modifications for SAR444245 and chemotherapy (reduction) 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, delay of IMP) or **dose omission** (ie, omission of any component of the IMP within a cycle) are permitted in case of TEAE. Dose modification will be made according to the worst grade of toxicity observed within a cycle. If a participant experiences several toxicities and

there are conflicting recommendations, the most conservative recommended dose adjustment should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

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

For cohorts B1 and B2, if a toxicity leads to SAR444245 discontinuation, pembrolizumab must be discontinued unless the TEAE leading to permanent IMP discontinuation is clearly attributable only to SAR444245, and patients have clinical benefit as determined by the treating physician. Participants who continue pembrolizumab in this scenario are informed as part of the initial consent process that pembrolizumab monotherapy is not a standard of care. For other cohorts, if any of the IMP components is permanently discontinued, the other IMP component can be continued until disease progression or other criteria as detailed in Section 7.1.1 are met. In this case it is partial permanent discontinuation and the end of treatment (EOT) assessment will be 30 days after the date of the last administration of the remaining IMP. When 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).

6.6.2 Cycle delay and dose omission

The treatment window is ±3 days for each of the Q3W administrations, and ±1 day for each nab-paclitaxel administration on Day 8 of the first 6 cycles. Within a cycle, a dose is deemed to have been delayed if the treatment is ≥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 6.6.3, Section 6.6.4, and Section 6.6.5. After treatment is withheld/cycle 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 or dose omission if toxicity occurs and the participant does not recover according to following rules:

- For nab-paclitaxel Day 1 and Day 8 administration in the first 6 cycles: 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.
- For Q3W IMP administration: If toxicity occurs and the participant does not recover on the day of planned administration or within the following 14 days, dose of a Q3W administered IMP may be omitted. Dose omitted for toxicity should not be replaced: restart of study IMPs could occur only on the initiation of the subsequent cycle.
- 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.

- IMP may be interrupted for situations other than TEAEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days of the scheduled interruption, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for interruption should be documented in the participant's study record.

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

Participants who experience Grade ≥3 treatment-related adverse events (TRAEs) at any time of the study (including clinically significant grade 3 laboratory abnormalities as defined in Section 10.3.1) will be required to temporarily withhold the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After treatment withhold, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline. Treatment resumption is at the discretion of the Investigator and Sponsor, if thought to be in the best interest of the participant, except when specified otherwise in this protocol, or if the event has required the IMP temporary interruption for more than 84 days from the last scheduled dose.

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

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

Dose reduction for SAR444245 from 24 µg/kg to ■ µg/kg (or another lower dose recommended by SB) may be decided when specified in the protocol or following discussions with the Sponsor.

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

Recommended guidelines for the management of specific adverse events including irAE, CRS, VLS and IRR are presented in Section 6.6.5.

6.6.4 Dose modification for chemotherapy

Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of chemotherapy throughout the course of the study for toxicities. Participants who require a third dose modification of any particular component will have that agent discontinued.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of multiple agents, all agents should be

reduced (if applicable), interrupted or discontinued according to the recommended dose modifications. Participants may have chemotherapy discontinued and continue on SAR444245/pembrolizumab. Similarly, participants may discontinue SAR444245/pembrolizumab and continue on chemotherapy alone if appropriate.

6.6.4.1 Dose modification for cisplatin, carboplatin and pemetrexed

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 7, Table 8, and Table 9. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Table 7 - Dose modification for chemotherapy agents

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m²	56 mg/m²	38 mg/m²	Discontinue
Carboplatin	AUC 5 Maximum dose 750 mg	AUC 3.75 Maximum dose 562.5 mg	AUC 2.5 Maximum dose 375 mg	Discontinue
Pemetrexed	500 mg/m²	375 mg/m²	250 mg/m²	Discontinue

Table 8 - Recommended dose modifications for chemotherapy hematological toxicity

		Pemetrexed	Cisplatin/Carboplatin
Platelets	**ANC**	**Dose level (DL) from Table 7**	
≥50 × 10^3 /uL AND	≥500 /uL	DL 0	DL 0
≥50 × 10^3 /uL AND	< 500 /uL	DL -1	DL -1
<50 × 10^3 /uL without bleeding AND	ANY	DL -1	DL -1
<50 × 10^3 /uL with Grade ≥2 bleeding AND	ANY	DL -2	DL -2
ANY AND	<1000/mm^3 + fever ≥38.5°C	DL -1	DL -1

Table 9 - Recommended dose modifications for chemotherapy non-hematological toxicity

		Pemetrexed	Cisplatin	Carboplatin
Event	**CTC Grade**	**Dose level (DL) from Table 7**		
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1	DL -1

6.6.4.2 Dose modification for nab-paclitaxel

Do not administer nab-paclitaxel on Day 1 of a cycle until ANC is at least 1500 /uL and platelet count is at least 100×10^3 /uL. In participants who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an ANC of at least 1500 /uL and platelet count of at least 100×10^3 /uL on Day 1 or to an ANC of at least 500 /uL and platelet count of at least 50×10^3 /uL on Day 8 of the cycle. Upon resumption of dosing, permanently reduce nab-paclitaxel dose as outlined in Table 10.

Withhold nab-paclitaxel for Grade 3-4 peripheral neuropathy. Resume nab-paclitaxel at reduced doses (see Table 10) when peripheral neuropathy improves to Grade 1 or completely resolves.

Table 10 - Recommended dose modifications for chemotherapy hematological and neurological toxicity

Event	Occurrence	Weekly nab-paclitaxel dose (mg/m²)
Neutropenic Fever (ANC <500 /uL with fever >38.5°C) OR Delay of next cycle by more than 7 days for ANC <1500 /uL OR ANC <500 /uL for more than 7 days	First	75
	Second	50
	Third	Discontinue nab-paclitaxel treatment
Platelet count less than 50 000/mm^3	First	75
	Second	Discontinue nab-paclitaxel treatment
Severe sensory neuropathy - Grade 3 or 4	First	75
	Second	50
	Third	Discontinue nab-paclitaxel treatment

Table 11 - Recommended dose modifications for chemotherapy non-hematological toxicity

Non-hematologic toxicity	Occurrence	Weekly dose of nab-paclitaxel (mg/m²)
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea Grade 3 mucositis ≥ Grade 3 peripheral neuropathy	First	75
	Second	50
Any other Grade 3 or 4 non-hematologic toxicity	Third	Discontinue nab-paclitaxel treatment
Grade 4 cutaneous toxicity, diarrhea or mucositis	First	Discontinue nab-paclitaxel treatment

6.6.5 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as AESIs, depending on grading according to NCI-CTCAE V5.0 (see Section 8.3.8). In case a specific adverse event meets the AESI definition it must be documented in the electronic case report form (e-CRF).

6.6.5.1 Infusion-related reactions (IRR)

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

An IRR 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 12.

Guidelines for the management of SAR444245 IRR events are provided in Table 13. 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.

Table 12 - Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild 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[a]. • 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.

a After an infusion-related reaction due to pembrolizumab infusion, 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

Table 13 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild 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.	Interrupt SAR444245 infusion. 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. 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	Permanently discontinue SAR444245. The participant can continue treatment with pembrolizumab. 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	Permanently discontinue SAR444245. The participant can continue treatment with pembrolizumab. 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.

6.6.5.2 Anaphylaxis

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of both SAR444245 and pembrolizumab and any chemotherapy 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 in 114, 115, 116).

6.6.5.3 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 ASTCT criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 14. 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 for 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 14. ASTCT CRS consensus grading scale is provided in Section 10.13.

Table 14 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended IMP dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245/pembrolizumab[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 both SAR444245 and pembrolizumab, 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.

Event severity (ASTCT CRS Consensus Grading)	Recommended IMP dose modification and supportive care guidelines
	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. IMP may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.
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, both SAR444245 and pembrolizumab should be temporarily withheld, 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. The participant can continue treatment with pembrolizumab without dose modification. <u>If CRS Grade 4, SAR444245 should be permanently discontinued and pembrolizumab temporarily withheld or permanently discontinued</u>. If temporarily interrupted, pembrolizumab can be resumed without dose modification only when symptoms have resolved or improved to Grade 1. 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 and pembrolizumab are 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.

6.6.5.4 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 administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 15. Of note, if the AE is considered immune-related, both drugs in the combination should be held according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed.

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

When SAR444245 or pembrolizumab can be restarted, they 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 15, 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.

Chemotherapy should be modified similarly as that for SAR444245 in case of irAE, ie withheld or permanently discontinued.

Table 15 - 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 resume 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	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		
Diarrhea/Colitis	Grade 2 or 3	Withhold	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		
AST or ALT elevation or Increased Bilirubin/hepatitis	Grade 2[a]	Withhold	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 returned to baseline or is stable).

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 3[b] or 4[c]	Permanently discontinue	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[d]	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 Withhold or permanently discontinue[d]	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 or permanently discontinue[d]	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 Permanently discontinue	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 Permanently discontinue	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	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.

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

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; IO=immuno-oncology; 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.

a 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.

b 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.

c 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.

d 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.

e Events that require discontinuation include but are not limited to: encephalitis, and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.5.5 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 10.13). 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 16. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 16 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended IMP dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	SAR444245[a] and pembrolizumab[a] should be withheld. Treatment with IV corticosteroids should be initiated as needed. SAR444245 and/or pembrolizumab may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. No modification in pembrolizumab dose is recommended, and consideration for reduction of SAR444245 dose to ■ µg/kg as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3 ICE score 1-2. 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 (>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 and pembrolizumab should be withheld. 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. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 14. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days 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 14. 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 and pembrolizumab are provided in the pharmacy manual
Abbreviations: AE = Adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; IV = Intravenous; NCI = National Cancer Institute.

6.6.5.6 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 17. 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 (117).

Table 17 - 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	IMP should be withheld. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg, and pembrolizumab[a] can be resumed without dose reduction. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, SAR444245 should be permanently discontinued. The participant can continue treatment with pembrolizumab upon resolution of the event or improvement to Grade 1. 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 and pembrolizumab are provided in the pharmacy manual.
Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

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

6.8 TREATMENT OF OVERDOSE

There is no specific antidote for overdose with SAR444245, pembrolizumab, or other anticancer therapies.

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 Section 6.6.5.4.

In the event of an overdose, the Investigator should:

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

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

- At the participant's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative. "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 patient to the patient's participation in the procedure(s) involved in the research.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Unacceptable AE.
  - Documented disease progression (including both radiological PD and clinical PD).
    - [redacted]
    - If a participant has PD per mRECIST and is clinically stable, it is at the discretion of the Investigator to continue treating the subject with the assigned treatment per protocol until pseudo-progression is ruled out. Radiological re-assessment should be done at least 4 weeks, but no longer than 8 weeks from the date of the scan suggesting progression of disease (Section 10.10.4). *Clinical Stability is defined as: 1) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) indicating disease progression. 2) No decline in ECOG performance status. 3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.*
  - Poor compliance to the study protocol.
  - Other, such as concurrent illness, that prevents further administration of study intervention, or that in the Investigator's opinion, in the best interest of the participant.
- In case of pregnancy occurrence.

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

7.1.1.1 Unacceptable adverse events leading to permanent intervention discontinuation

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Table 15, or if the Investigator believes that it is in best interest of the participant.

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

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

Decision criteria for discontinuation following immune-mediated AEs are described in Section 6.6.5 (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 10.11; Appendix 11: Contingency Measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

7.1.3 Rechallenge

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

Recommendations for rechallenge in the context of an epidemic/pandemic (eg, COVID-19) are included in Appendix 11 Contingency Measures for a regional or national emergency (Section 10.11) that is declared by a governmental agency.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

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

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

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

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

7.3 LOST TO FOLLOW UP

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures are summarized in this section and their timing is presented in the SoA (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.
- 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 10.11.

8.1 EFFICACY ASSESSMENTS

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

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

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 (for NSCLC) or mRECIST (for mesothelioma) (see Section 10.8 and Section 10.10) 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 (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. Participants 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. 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 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 and [redacted]

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).

[redacted]

mRECIST

Tumor evaluation will be assessed by the investigator using mRECIST criteria for mesothelioma (Section 10.10).

To account for the possibility of unconventional immune responses, participants may continue treatment beyond progression if pseudo-progression is ruled out after discussion and approval from the Sponsor.

Any participant who experiences best response (PR or CR) after initial progression in the context of continued treatment (according to principles of pseudo-progression and after Sponsor approval) will not have that best response (partial or complete) counted towards the primary endpoint of this study.

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. Combining SAR444245 with other anticancer therapies may increase the frequency and severity of irAEs related to other anticancer therapies. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level

will be monitored. When clinically indicated, on-treatment ECG and LVEF will be assessed and compared to baseline. More details on the safety assessment are provided below. Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

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

8.2.2 Vital signs

- Vital signs including temperature, pulse rate, respiratory rate and blood pressure will be measured after 5 minutes rest.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively;
  - **For the safety run-in participants** vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an in-patient setting.
  - **For other participants**, vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose. At Investigator's discretion, participants (not in the safety run-in) may have intensive vital sign monitoring.
- From Cycle 2 and beyond, study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.

8.2.3 Electrocardiograms and LVEF

- Includes single 12-lead ECG and LVEF that will be performed at screening and then, as clinically indicated.

- Triplicate 12-lead ECG will be obtained when indicated, for instance to further document a QTc prolongation, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- Each time a triplicate ECG is required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- LVEF evaluation will be done by echocardiography or multigated acquisition (MUGA), and any repeated assessment should be done with the same technology used at screening.
- Additional evaluations such as unscheduled ECG, LVEF, Holter monitoring, cardiac enzymes and consultation with a cardiologist should be done when clinically indicated.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and 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. 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.
  - 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 08 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 150 days (for Cohorts A1, A2, B1, B2 and C1) or 420 days (for Cohort A3) after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

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

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

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 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Stabilization is defined as an AE ongoing without any change for at least 3 months. Participants with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or starting of a new antineoplastic therapy, whichever occurs first.

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

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of 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 and country-approved product labeling for pembrolizumab).
    - 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 150 days (for Cohorts A1, A2, B1, B2 and C1) or 420 days (for Cohort A3), following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates another anticancer therapy.

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

8.3.6 Cardiovascular and death events

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

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

Not applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

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

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.3).
  - In the event of pregnancy in a female participant, IMP should be discontinued.

  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 10.4).

- Symptomatic overdose (serious or nonserious) with IMP/NIMP (excluding pembrolizumab)
  - 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.
- Symptomatic or asymptomatic overdose with pembrolizumab:
  - An overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥5 times the indicated dose.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*.

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

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

8.3.9 Guidelines for reporting product complaints

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

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

8.4 PHARMACOKINETICS

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.

Non-compartmental analysis of SAR444245 plasma concentrations will be conducted where applicable. Plasma concentrations of SAR444245 will be analyzed in a popPK modelling framework and reported separately. In this context, further exposure-response analysis may be conducted.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for details of pharmacodynamics biomarker.

8.6 GENETICS AND/OR PHARMACOGENOMICS

[redacted]

[redacted]

8.7 BIOMARKERS

[redacted]

8.8 IMMUNOGENICITY ASSESSMENTS

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

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

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

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

8.9 HEALTH ECONOMICS

No health economics data will be collected.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

All 6 cohorts of the study are designed to obtain antitumor activity, safety, PK, and pharmacodynamic (PDy) data on SAR444245 administered in combination with pembrolizumab with or without different anticancer agents.

The study is designed to assess clinical benefit of SAR444245 when combined with pembrolizumab in participants with lung cancer or pleural mesothelioma. As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design. No formal testing procedure is going to be considered.

9.2 SAMPLE SIZE DETERMINATION

The study will start with a safety run-in to confirm the dose of SAR444245 when combined with other anticancer therapies in a sample of at least 6 participants in each study intervention.

Overall in the core phase (all cohorts), the plan is to treat approximately 40 participants at the confirmed safe dose per cohort.

In the expansion phase (Cohort B only), approximately 57 participants are planned to be treated at the confirmed safe dose per cohort.

Core Phase

Table 18 lists estimated ORR and the corresponding 90% exact CIs by number of responders in each cohort.

Table 18 - Estimated objective response rate (ORR) and 90% CI for core phase

Number of responders (N=40)	ORR	90% CI for ORR (Clopper-Pearson)
6	15.0%	(6.7%, 27.5%)
7	17.5%	(8.5%, 30.4%)
8	20.0%	(10.4%, 33.2%)
9	22.5%	(12.3%, 36.0%)
10	25.0%	(14.2%, 38.7%)
11	27.5%	(16.3%, 41.4%)
13	32.5%	(20.4%, 46.6%)
15	37.5%	(24.7%, 51.7%)
17	42.5%	(29.2%, 56.7%)
19	47.5%	(33.8%, 61.5%)
24	60.0%	(45.8%, 73.1%)

Expansion Phase (Only for Cohort B1 and/or Cohort B2)

At the end of the core phase of Cohorts B1 and B2, the overall efficacy and safety profile will be assessed. The Sponsor may decide to open a 57-participant expansion phase based on the totality of data from the core phase if the posterior probability that the true ORR is greater than 23%, which is considered minimal efficacious signal of interest, is greater than 80% with durable response. Based on a conjugate non-informative prior of beta (0.5, 0.5) at the time of the design of the study, at least 12 responders out of 40 exposed participants at the confirmed safe dose (ORR=30%) need to be observed in the core phase. However, emerging data generated from outside of the study may warrant a different prior to be considered before the formal IA. Analyses based on the total 97 participants at the confirmed safe dose by combining the core phase and expansion phase will be performed for each cohort. Table 19 lists estimated ORR and the corresponding 95% exact CIs by number of responders from a sample size of 97 participants evaluable for activity in each cohort.

Table 19 - Estimated objective response rate (ORR) and 95% CI for Cohorts B1 and B2 (combining core and expansion phases)

Number of responders (N=97)	ORR	95% CI for ORR (Clopper-Pearson)
10	10.3%	(5.1%, 18.1%)
15	15.5%	(8.9%, 24.2%)
20	20.6%	(13.1%, 30%)
25	25.8%	(17.4%, 35.7%)
28	28.9%	(20.1%, 39%)
30	30.9%	(21.9%, 41.1%)

With a sample size of 40 study participants at the confirmed safe dose in the core phase, 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. With a sample size of 97 study participants in total, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 62.3%, 85.9%, or >99%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this study.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 20):

Table 20 - 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).

Population	Description
Efficacy	Efficacy population will include all participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.
DLT-evaluable	DLT-evaluable population will include all exposed participants in the safety run-in who have been observed for at least 21 days. Any participant who experienced a DLT during DLT observation period will also be DLT-evaluable
PK	The PK population will include all participants from the exposed population with at least 1 PK concentration available after the first dose of study intervention.
PDy	The PDy population will include all participants from the exposed population with at least 1 PDy parameter assessed after the first dose of study intervention.

9.4 STATISTICAL ANALYSES

The statistical analysis plan 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, and 90% confidence interval (CI) will be provided for primary and secondary efficacy endpoints for descriptive purpose only.

All efficacy analyses will be performed on the efficacy population and analyzed by cohort and by dose (as applicable). Some cross-cohort summaries will be presented too. For Cohorts B1 and B2, results will be presented by core phase and overall phase (combining core phase and expansion phase). Objective response rate, as well as PFS, DoR, and CBR will be derived using the local radiologist's/Investigator's assessment for all cohorts. Central imaging may be done retrospectively if significant activity is observed. The assessments for Cohort C1 are based on mRECIST and all other 5 cohorts will use RECIST 1.1.

All safety analyses will be performed on the exposed population by cohort, by dose (if applicable) and overall (if applicable). Baseline values 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)

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 anticancer therapy, whichever occurs first. The BOR will be summarized with descriptive statistics. The Objective Response Rate (ORR) is defined as the percentage of participants from the analysis population with BOR is either CR or PR assessed per investigators. The ORR will be summarized with descriptive statistics and the corresponding two-sided 90% CIs calculated from Clopper-Pearson exact method will be also presented. 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 efficacy (DoR, CBR, PFS, TTR), safety, immunogenicity, and PK.

9.4.3.1 Time to response

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

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

9.4.3.2 Duration of response

The DoR will only be analyzed on the subgroup of participants who have achieved confirmed objective response. The DoR will be defined as the time from the date of first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed to the date of first documentation of objective PD before the initiation of any post-treatment anticancer therapy or death due to any cause, whichever occurs first.

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

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 and classified by SOC and Preferred Term (PT) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Immune cell-associated neurotoxicity syndrome and CRS events will be graded using ASTCT Consensus Grading and will be summarized separately.

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

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

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

Treatment-emergent adverse events:

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

- TEAEs.
- TEAEs of Grade ≥3.
- Grade 5 TEAE (any TEAE with a fatal outcome during the on-treatment period).
- Serious TEAEs.
- Serious treatment-related TEAEs (for each individual drug).

- TEAE leading to partial intervention discontinuation.
- TEAE leading to full intervention discontinuation.
- Treatment-related TEAEs (for each individual drug).
- Treatment-related TEAEs of Grade ≥3 (for each individual drug).

Number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE V5.0 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 related to each individual drug, TEAEs leading to partial intervention discontinuation, TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.

The following deaths summaries will be generated:

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

9.4.3.6 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.

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

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V5.0, 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.

When the NCI-CTCAE V5.0 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 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]

9.4.4.2 Biomarker endpoints

[redacted]

9.4.5 Other safety analyse(s)

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

9.4.6 Other analyse(s)

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.11.

9.5 INTERIM ANALYSES

During the core phase, no formal interim analyses are planned. However, the following analyses will be performed:

- At the end of the safety run-in of each regimen, the occurrence of DLT and other safety data will be reviewed by SB to decide about continuation of the dose of SAR444245 of 24 µg/kg or reduction to [redacted] or another lower dose level.
- After the dose is confirmed by the SB, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the Independent Data Monitoring Committee (IDMC). The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. IDMC will review safety data periodically. Ad hoc IDMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other SAR444245 studies. The IDMC procedures will be detailed in the IDMC charter and approved by the IDMC members.

In addition, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the study, eg, in each cohort, after 20 participants at the confirmed safe dose have undergone two post-baseline tumor assessments (approximately 18 weeks from the 20 participants are first treated) or have discontinued study treatment, whichever is earlier.

At the end of the core phase, cohorts B1 and B2 will have one formal interim analysis when all participants in the core phase have at least 2 post-baseline tumor assessments or discontinued study treatment (whichever occurs first). The Sponsor will decide if the expansion will be initiated based on totality of the data observed.

Therefore, for Cohort A1, Cohort A2, Cohort A3 and Cohort C1, the cohort cut-off for the primary ORR endpoint analyses is estimated to be approximately 9 months from the date of the last participant's first infusion in the core phase (to document that last participant response is maintained for 6 months in the core phase). For Cohort B1 and Cohort B2, the cohort cut-offs for the analyses are as follows:

- IA cut-off: the date on which all participants in the core phase have at least 2 post-baseline tumor assessments or discontinue study treatment (whichever occurs first).
- Primary analysis cut-off: the date on which the last participant response is maintained for 6 months in the expansion phase (approximately 9 months from the last participant's first infusion in the expansion phase).

For each cohort, the cut-off date for the final analysis will be 3 years from the date of cohort last-patient-in, or when all patients within the cohort have completed the study.

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, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

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

The ICF contains a separate section that addresses the use for research of participants' data and/or leftover biological samples. This future research is described in Core Study Informed Consent Form (CSICF) Part 2. The option to participate in future research 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 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 11: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.11).

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 phamaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Independent Data Monitoring Committee

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 21 will be performed by local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 21 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology[a]	Platelet count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Urea or blood urea nitrogen (BUN)
	Creatinine and eGFR (MDRD formula[b])
	Glucose
	Potassium
	Sodium
	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
Endocrine function tests[d]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT])
Routine urinalysis	• Specific gravity, pH, glucose, protein, blood, ketones, and leukocytes by dipstick. • Microscopic examination (if blood or protein is abnormal).

Laboratory assessments	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]. • The results of each test must be entered into the e-CRF. • See additional requirement specific to Japan in Section 10.7

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, D2, D8 and D15 during Cycle 1, then on Day 1 of every cycle up to Cycle 12, then every other cycle during Treatment Phase. For participants in the safety run-in, it will be also performed at D3. During the Observation Period, it will be performed at Follow-Up Visit 1. It can also be performed as clinically indicated. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

b Modification of Diet in Renal Disease (MDRD) equation: Glomerular filtration rate (mL/min/1.73 m^2) = 175 × (Serum Creatinine)-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 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.

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 150 days (for Cohorts A1, A2, B1, B2 and C1) or 420 days (for Cohort A3) 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 serology at screening will be tested in any countries where mandatory as per local requirements. See requirements specific to Japan in Section 10.7.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

A) Results in death.

B) Is life-threatening

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

C) Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

D) Results in persistent or significant disability/incapacity

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

E) Is a congenital anomaly/birth defect.

F) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm,
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),

- Convulsions (seizures, epilepsy, epileptic fit, absence, etc),
- Development of drug dependence or drug abuse,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions.

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

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

AE and SAE recording

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

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, as per NCI CTCAE V5.0 definitions:

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

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

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the 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 a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

- New or updated information will be recorded in the originally 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's representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator study file.

SAE reporting to the Sponsor's representative via paper 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 criterion I 08.

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.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
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

Use/Analysis of DNA/RNA

[redacted]

[redacted]

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

France

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

Section 5 Study population

For Cohort A1: French patients with potential risk of rapidly progressing disease (eg, high tumor burden, tumor with risk of mediastinal or spinal cord compression, or rapidly growing tumor) will be excluded.

For Cohort A2: French patients will be excluded.

For Cohort A3: French patients will not be considered for safety run-in. ANSM approval will be required before opening this cohort.

Japan

Section 1.3 Schedule of Activities (see Section 1.3)

All Japanese patients must be hospitalized until Cycle 1 Day 8, and participants can be discharged if physician-in-charge judges no significant safety concerns for discharge based on the available safety data until the day of discharge (eg, vital signs, physical examination/signs, symptoms, blood hematology, and blood chemistry).

Section 1.5 Pharmacokinetic Flowchart (see Section 1.5)

All Japanese patients are subject to the intensive PK sampling as shown in Table 22.

Table 22 - Japanese participants enrolled in either Cohorts B1 or C1

Cohort	Japanese participants of EITHER B1 OR C1 (SAR444245 + pembrolizumab)																				
Cycle	**Treatment Cycle 1**										**Treatment Cycle 2**		**Treatment Cycle 4**						**Treatment Cycle 7, 10 + every 5th cycle**		**EOT visit**
Day	**D1**						**D2**	**D3**	**D4**	**D8**	**D1**		**D1**						**D1**		**30 (±7) days after last IMP admin**
Time after start of SAR444245 dosing [h]	**SOI**	**EOI**	**1**	**2**	**4**	**8**	**24**	**48**	**72**	**any time**	**SOI**	**EOI**	**SOI**	**EOI**	**1**	**2**	**4**	**8**	**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	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			
SAR444245 ADA sample ID	AB00[a]								-	AB01	AB00[a]		AB00[a]						AB00[a]		ABF00

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

b P01 samples = End of infusion (EOI) sample. Must be taken at end of infusion precisely.

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 1 h, 2 h, 4 h, 8 h, (24 h, 48 h and 72 h for Cycle 1) 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 for Cycle 1) after end of resumed infusion (as per protocol).

ADA = Anti-drug antibodies; D: day; EOT: end of treatment; PK = Pharmacokinetic.

Section 5.1 Inclusion Criteria (see Section 5.1)

The following underlined wording is added to the inclusion criteria:

I 07. For participants in Cohorts B1 and B2 - Based on the Investigator's judgment, at this time, either docetaxel or pemetrexed, or other local standard of care is not the best treatment option for this specific participant. The eligibility of participant to take part in the study will be validated at the multidisciplinary collegial meeting in countries listed in Section 10.7 of the protocol.

I 08. B) Female participants

A female participant is eligible to participate if she is not pregnant or breastfeeding (including breastfeeding woman who will stop breastfeeding), and at least one of the following conditions applies:

Section 6.5.1 Acceptable Concomitant Medications (see Section 6.5.1)

The following local regulatory requirement should be noted.

Colony-Stimulating Factors

- Granulocyte macrophage colony-stimulating factor, and macrophage colony-stimulating factor are not indicated for neutropenia caused by cancer chemotherapy.

Section 10.2 Appendix 2 Clinical Laboratory tests, Table 21 (see Table 21)

The following local regulatory requirements should be noted.

Other screening tests

To identify interstitial lung disease during screening period, and for early detection of interstitial lung disease after IMP initiation when clinically indicated, tests such as chest X-ray and sialylated carbohydrate antigen KL-6 may be performed (in addition to scheduled CT scan, vital sign, and blood test).

footnote f

- Screening and monitoring for hepatitis B virus are performed based on the Guidelines for Prevention of Hepatitis B Induced by Immunosuppression and Chemotherapy in the JSH Guidelines for the Management of Hepatitis B Virus Infection (120).

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

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

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

Selection of Lesions

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

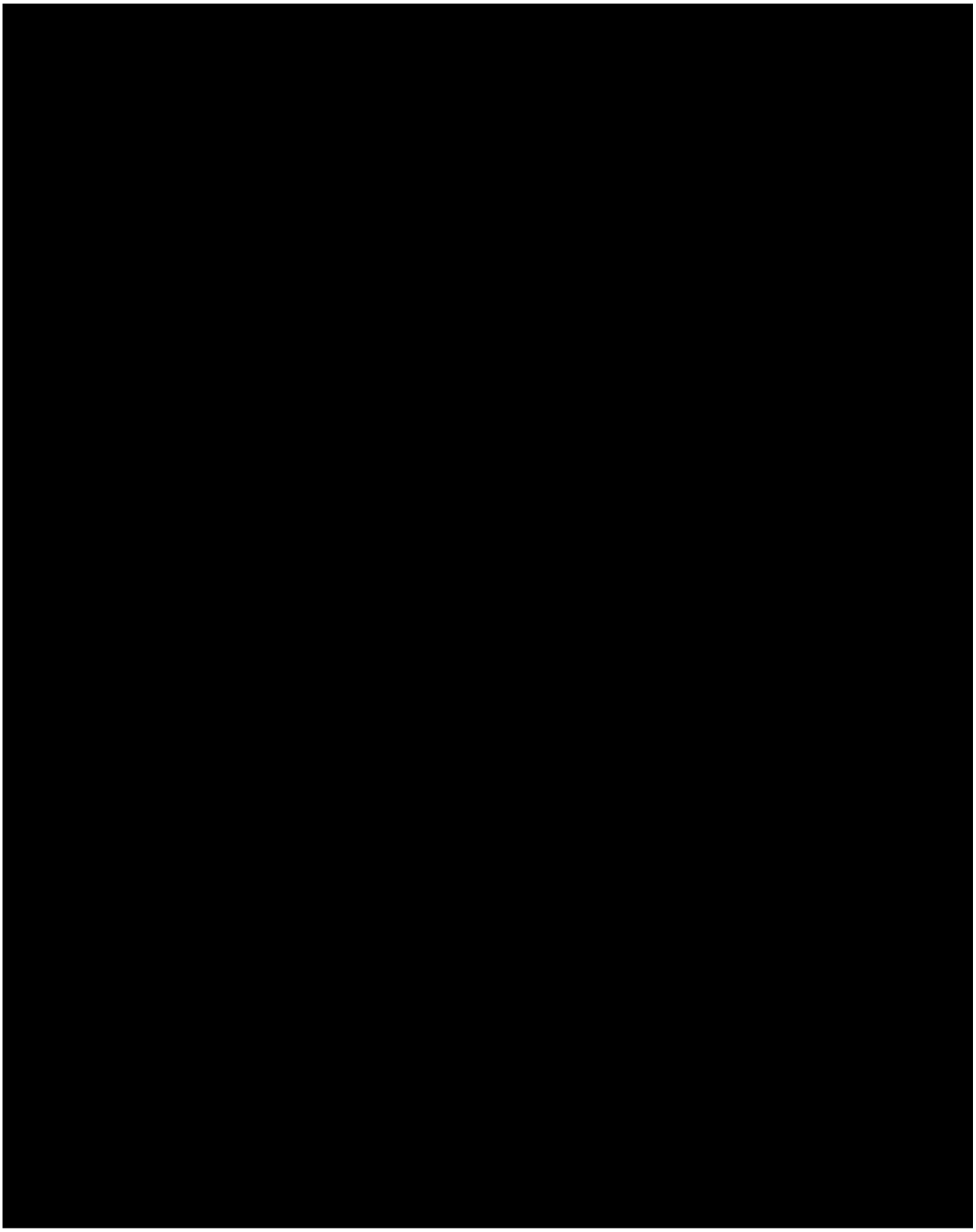
Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

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: [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 (1). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

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

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

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

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

10.10 APPENDIX 10: MODIFIED RECIST CRITERIA FOR MESOTHELIOMA

Tumor response will be assessed by the investigator using modified RECIST Criteria for Mesothelioma (2, 121).

10.10.1 Target lesion measurements

Uni-dimensional measurement for tumor lesion around the pleural surface

Unidimensional measurements of tumor thickness perpendicular to the chest wall or to the mediastinum should be performed in **2 sites (on the same slice interval)** at **3 separate levels** on CT scan. At least one of these unidimensional measurements must have a thickness of at least 10 mm.

In order to allow reproducible assessment at different time-points, CT scan cuts should be chosen at least **1 cm apart** and related to anatomical landmarks in the thorax (preferably above the level of division of the main bronchi). At re-assessment, pleural thickness must be measured at the same position and level. Whether possible, subsequent tumor reassessment should be performed by the same observer.

The sum of these **6 measurements** = one **pleural uni-dimensional measure**.

Uni-dimensional measurement for other tumor lesions

Nodal, subcutaneous and other bi-dimensionally measurable lesions are measured uni-dimensionally as per RECIST 1.1.

Total tumor measurement

Uni-dimensional measures of nodal lesions are added to the pleural uni-dimensional measure to obtain the total tumor measurement.

10.10.2 Non-target lesion measurements

Non-target lesions are defined as per RECIST 1.1 (eg, pleural effusion). Re-appearance or increase of pleural effusion will require further investigations (including pleuroscopy to affirm progression if judged necessary by investigator).

10.10.3 Definitions of response

- The overall tumor response is defined per RECIST 1.1.

10.10.4 Pseudo-progression

Pseudo-progression is defined as radiological tumor growth, followed by disease stability or tumor shrinkage. An unconventional pattern of response should meet the following criteria (4, 93). Re-assessment to rule out pseudo-progression should be done at least 4 weeks, but no more than 8 weeks from the initial radiological evidence suggesting progression.

Patients who had not experienced a best overall response of partial or complete response prior to initial RECIST 1.1-defined progression, and met at least one of the following:

- Appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions. Or
- Initial increase from nadir ≥20% in sum of target lesions followed by reduction from baseline of at least 30%. Or
- Initial increase from nadir ≥20% in sum of target lesions followed by at least 2 tumor assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions.

10.11 APPENDIX 11: 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).

10.11.1 Informed consent

The participant or their legally authorized representative 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).

10.11.2 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.

10.11.3 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.

10.11.4 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.

10.12 APPENDIX 12: RISK ASSESSMENT

The information shown in Table 23 reflects the clinical safety data currently available in the SAR444245 IB. For pembrolizumab, the information below is per currently available USPI and EU SmPC. Please always refer to the latest version of the SAR444245 IB and pembrolizumab local label for the most up-to-date safety data.

Table 23 - 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 have reported such AE as detailed in the SAR444245 IB. Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.	SAR444245 Standard pre-medication Dose modification and treatment guidelines for SAR444245 infusion-related reactions are provided in Table 13. Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion-related reactions are provided in Table 12.
Hypersensitivity, including anaphylaxis	SAR444245 Not observed in non-clinical toxicology studies. No reports of anaphylaxis in the HAMMER study to date. Pembrolizumab Not specifically reported, but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to or contraindication for any components of SAR444245, PEG, pegylated drugs or pembrolizumab.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
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. Pembrolizumab Common: pneumonia.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Signs and symptoms of infection are monitored as part of TEAE.
Cytokine release syndrome	SAR444245 No major increases in cytokines have been reported in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported such AE as detailed in the SAR444245 IB. Pembrolizumab Not specifically reported.	Study to be conducted at sites experienced with CRS management, with bed available in ICU. 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 Table 14.
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 Table 17.
Hematological/bone marrow toxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, SAR444245-related changes in clinical pathology parameters were observed at all doses and were generally most prominent 3 days following each dose. Changes in hematology parameters included decreased or attenuated reticulocytes followed by decreases in red blood cell (RBC) mass at [redacted] mg/kg/dose, and increased WBCs (lymphocytes and monocytes) and transiently mildly decreased platelets at [redacted] mg/kg/dose. The increases in lymphocytes were attributed to the expected pharmacology of SAR444245 and correlated with the gross and microscopic findings of splenic and lymph node enlargement and increased lymphoid cellularity; there were no microscopic or clinical correlates for the decreases in platelets. Adverse events of bone marrow toxicity have been reported in the HAMMER study and are presented in the SAR444245 IB.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Dose modification/discontinuation of IMP for Grade 3/4 anemia, thrombocytopenia and/or neutropenia as per general guidelines for the management of TRAEs (see Section 6.6.3).

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 IB. Pembrolizumab Pembrolizumab can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of pembrolizumab in 0.2% of patients and withholding of pembrolizumab in 0.3% of patients. All patients who were withheld reinitiated pembrolizumab after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.	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 provide under immune-related reactions in Table 15.
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. Pembrolizumab Common: nephritis, acute kidney injury.	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 provide under immune-related reactions in Table 15.
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 μg/kg monotherapy) associated with neurological manifestations [hypertension, chills/rigors, flushing, fever (maximum temperature: 102.8°F), as well as	Exclusion of participants with active brain metastases or leptomeningeal metastases. See E 03 for details. Guidelines for the management of ICANS are provided in Table 16

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	neurological symptomatology (loss of ability to follow commands, confusion, aphasia, and involuntary fist clinching)] was reported in the HAMMER study. The event resolved completely within 30 to 60 mins after treatment with tocilizumab and steroid. This patient later discontinued the study.	
	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy. Uncommon: epilepsy.	
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 IB. Pembrolizumab Combination with chemotherapy, common: hypertension, cardiac arrhythmia (including atrial fibrillation).	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 10 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. Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	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).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		Close monitoring for endocrine abnormalities and other potentially autoimmune phenomena will be performed. Dose modification and treatment guidelines for immune-related reactions are provided in Table 15.
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. Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	Exclusion of participants who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial as per inclusion criterion I 08. Guidance on highly effective contraceptive methods is provided in the protocol. Pregnancy tests are to be performed regularly as described in Section 8.2.5.
Use in children	The safety and efficacy of the study interventions in children below 18 years of age have not yet been established.	Exclusion of participants under 18 years of age.
Participants over 75 years of age	SAR444245 At this stage of development, no safety data are available for this population.	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%) (122, 123, 124).	Strict adherence to the protocol. Adequate and verified training of staff at investigational sites.
Overdose and its treatment	There is no specific antidote for overdose with SAR444245. No specific information is available on the treatment of overdose of pembrolizumab.	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

10.13 APPENDIX 13: ASTCT ASSESSMENT FOR ICANS AND CRS

Table 24 - 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
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: (3).

Table 25 - 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: (5).

Table 26 - 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: (3)

10.14 APPENDIX 14: ABBREVIATIONS

1L: first-line
2/3L: second- or third-line
ADA: anti-drug antibody
ADL: activities of daily living
AE: adverse event
AESI: adverse event of special interest
ALT: alanine aminotransferase
ART: anti-retroviral therapy
ASCO: American Society of Clinical Oncology
AST: aspartate aminotransferase
ASTCT: American Society for Transplantation and Cellular Therapy
BOR: best overall response
CBR: clinical benefit rate
CI: confidence interval
CLS: capillary leak syndrome
CR: complete response
CRF: case report form
CRS: cytokine release syndrome
CSFs: colony-stimulating factors
CT: computed tomography
[redacted]
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
[redacted]
DLT: dose-limiting toxicity
DoR: duration of response
ECG: electrocardiogram
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
EOT: end of treatment
ESMO: European Society for Medical Oncology
FU: Follow-up visit
HCV: hepatitis C virus
IB: Investigator's Brochure
ICANS: immune cell-associated neurotoxicity syndrome
ICI: immune checkpoint inhibitor
IDMC: Independent Data Monitoring Committee
IHC: immunohistochemistry
IL: interleukin
IMP: investigational medicinal product
irAE: immune-related adverse event
[redacted]
IRR: infusion-related reaction

MPM:	malignant pleural mesothelioma
mRECIST:	Modified response evaluation criteria in solid tumors
MRI:	magnetic resonance imaging
MTD:	Maximum Tolerated Dose
mTPI2:	modified toxicity probability interval 2
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP:	non-human primate
NIMP:	non-investigational medicinal product
NK:	natural killer
NSAIDs:	nonsteroidal anti-inflammatory drugs
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
[redacted]	
OTC:	over-the-counter
PD:	progressive disease
PD1:	programmed cell death protein 1
PD-L1:	programmed cell death-ligand 1
PDy:	pharmacodynamic
PFS:	progression free survival
PK:	pharmacokinetic
PO:	oral route
PR:	partial response
PT:	preferred term
Q2W:	every 2 weeks
Q3W:	every 3 weeks
RCC:	renal cell carcinoma
RECIST:	response evaluation criteria in solid tumors
RP2D:	recommended Phase 2 dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SB:	Study Board
SD:	stable disease
SmPC:	Summary of Product Characteristics
SOC:	standard of care
SpO2:	oxygen saturation
TCR:	T cell receptor
TEAEs:	treatment-emergent adverse events
TIL:	tumor infiltrating lymphocytes
TLS:	tumor lysis syndrome
[redacted]	
TME:	tumor microenvironment
TPS:	tumor proportion score
T-regs:	regulatory T-cells
ULN:	upper limit of normal
UPM:	unit probability mass
VLS:	vascular leak syndrome

WOCBP: woman of childbearing potential

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01 (19 March 2021)

This amended protocol (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 rationale for the amendment is to clarify criteria for cytokine release syndrome reporting and simplify the Independent Data Monitoring Committee set-up.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Footnote n has been updated to add that CRS will be graded using ASTCT criteria integrated with central laboratory cytokine results	To clarify CRS grading criteria for reporting
1.4 Biomarker flowchart	Clarified that every effort should be made to obtain a cytokine sample for an event of CRS of any grade	To facilitate comprehensive CRS reporting
6.6.5.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	Clarified that central laboratory cytokine results will be integrated into the grading of CRS events and the guidelines provided are for any suspected CRS event	To facilitate comprehensive CRS reporting
9.5 Interim analyses	The frequency of Independent Data Monitoring Committee review was revised	To simplify the Independent Data Monitoring Committee set-up

Amended protocol 02 (05 May 2021)

This amended protocol for Review (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 primary reason for the amendment is to respond to Health Authority requests for correction and clarification. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 4.1 Overall Design	The wording concerning the number of participants in the safety run-in has been clarified.	Regulatory Authority (FDA) request and to improve clarity
Section 1.1 Synopsis: Overall design, Section 4.1 Overall Design, and Section 9.3 Populations for Analyses (Table 19)	The following text has been deleted: "and have received at least 80% of the intended Cycle 1 dose".	Regulatory Authority (FDA) request and for clarification
Section 1.1 Synopsis, Section 4.1 Overall Design, and Section 5.1 Inclusion criteria	For Cohorts B1 and B2, the following text "Participants must have clinically benefitted but later experienced disease progression on an anti PD1/PD-L1-based regimen and no more than 1 chemotherapy regimen (detailed in Section 5.1 Inclusion Criteria I 06) to treat their NSCLC to be eligible)" has been removed for clarity. Eligibility criterion I06 for Cohorts B1 and B2 was changed to include participants for enrollment who experienced disease progression on or after one platinum-based chemotherapy which is either given as part of the anti-PD1/PD-L1 containing regimen, or as a separate regimen.	Regulatory Authority (FDA) request
Section 1.1 Synopsis and Section 6.1.2.2 Premedication for pemetrexed	In the instructions regarding premedication for pemetrexed, text was revised to clarify that folic acid dosing should be daily.	Change made for clarification
1.3 Schedule of activities (SoA) (footnote q) and 8.1.1 Assessment of objective response using the most appropriate modality according to the nature of the measurable lesion(s)	The text "If lesions are identified, the lesions must be treated, regardless of symptoms" has been deleted and replaced with "Participants 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. In all other cases, the lesions must be treated".	Change made to be consistent with exclusion criterion E03

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
Section 4.1 Overall Design: Dose limiting toxicity	The following DLT criteria have been added as follows: • Any Grade 3 non-hematologic laboratory value Exceptions: - Grade 3 electrolyte abnormalities that are not clinically complicated and resolve within 72 hours with conventional medical interventions. - Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis. • Any Grade 4 non-hematologic laboratory value • Other Abnormalities: - Any death not clearly due to the underlying disease or extraneous causes - Any toxicity requiring permanent discontinuation of the study drug(s). The following DLT criteria has been changed from: • Grade 3 or above AE that does not resolve to grade ≤2 within 7 days of starting accepted standard of care medical management To • Other Grade 3 or above AE except: - Grade 3 fatigue that resolves within 1 week. - Grade 3 nausea, vomiting, or diarrhea that resolves within 72 hours with antiemetics and standard supportive care measures. The following DLT criteria have been removed: "The following non-hematologic AEs are exceptions: Grade 3 or 4 laboratory abnormalities that are not clinically significant per recruiting Investigator and Sponsor".	Regulatory Authority (FDA) request and to clarify DLT criteria
Section 4.1 Overall Design: Study Committee	The following text has been added: "After safety run-in dose confirmation, occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants per regimen will trigger SC to rapidly convene to assess safety or need to pause enrollment to allow for a safety review. SC (during safety run-in), IDMC (during core phase and expansion) and Sponsor can decide to stop any cohort in case of excessive toxicity (for example but not limited to excessive irAE or excessive number of G4/5 events) is observed".	Regulatory Authority (FDA) request, and to clearly define study stopping rules and provide a rate of adverse events (AEs) resulting in a pause in study enrollment, and to allow the Study Committee (SC) to review the safety data before study enrollment may resume.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria and Section 6.5.2 Prohibited Concomitant Medications	E15 and text in Section 6.5.2 were updated to include live-attenuated virus vaccines	Changes made for clarification
Section 6.6.1 General rules	The following text has been added: "For cohorts B1 and B2, if a toxicity leads to SAR444245 discontinuation, pembrolizumab must be discontinued unless the TEAE leading to permanent IMP discontinuation is clearly attributable only to SAR444245, and patients have clinical benefit as determined by the treating physician. Participants who continue pembrolizumab in this scenario are informed as part of the initial consent process that pembrolizumab monotherapy is not a standard of care".	Regulatory Authority (FDA) request and to clarify that participants enrolled in B1 or B2 cohorts are adequately informed that continuation of pembrolizumab monotherapy after SAR444245 discontinuation is not a standard of care.
	The sentence "When both IMP components are permanently discontinued it is full permanent discontinuation" was revised to "When all IMP components are permanently discontinued it is full permanent discontinuation.	Change made for accuracy
Table 8 and Section 6.6.4.2 Dose modification for nab-paclitaxel	Units for platelet count were corrected	Change made for correction
Section 6.6.5.1 Infusion-related reactions (IRR)	The following text has been highlighted in bold in Table 11: "Participant is permanently discontinued from further study drug treatment".	Regulatory Authority (FDA) request, for clarification, and to align with current pembrolizumab standard text.
	In Table 11, "interrupt" has been changed to "stop".	
Section 6.6.5.4 Immune-related adverse events	Table 14 has been updated to add instructions regarding immune-related adverse events of Neurological Toxicities and Exfoliative Dermatologic Conditions. An abbreviations list and a note stating "Non-irAE will be managed as appropriate, following clinical practice recommendations" have been added to the footnote. In footnote e, the events of "Guillain-Barre Syndrome, Stevens-Johnson Syndrome and toxic epidermal necrolysis" were removed and replaced by "and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis)"	To align with current pembrolizumab standard text.
Section 8.2.2 Vital signs	Collection of vital signs including timing and in/out-patient settings has been clarified for participants in the safety run-in and other cohorts at Cycle 1 and beyond.	Regulatory Authority (FDA) request
	The requirement to measure vital signs in a semi-supine position has been removed	To simplify instructions
Section 8.3.1 Time period and frequency for collecting AE and SAE information	The following text has been added to specify the collection of all immune-related adverse events (irAEs) until 90 days:	Regulatory Authority (FDA) request
	"This does not include irAEs, which will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated."	

Section # and Name	Description of Change	Brief Rationale
Section 8.4 Pharmacokinetics	Added clarification on pharmacokinetics (PK) analysis plan.	Regulatory Authorities (FDA) request
Section 9.2 Sample size determination: Expansion Phase (Only for Cohort B1 and/or Cohort B2)	"The posterior probability that the true ORR is greater" has been changed from 20% to 23% to align with the ORR from the combination therapy of docetaxel and ramucirumab. The minimum number of responders has been amended from 11 to 12. The ORR has been changed from 27.5% to 30%.	Regulatory Authority (FDA) request
Section 9.4.3.4 Progression-free survival	The following text was revised: 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 ~~when relevant~~, or death due to any cause, whichever occurs first.	Change made for clarification
10.1.9 Study and site start and closure	The following information was added: If the study is early terminated the patients who are receiving and benefitting from study treatment as per Investigator judgment may continue study treatment until protocol defined treatment discontinuation criteria are met. The patients who continue study treatment after early study termination should be followed for safety (i.e. 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.	Change made for clarification
10.7 Appendix 7 Country-specific requirements	Instructions specific to participants from Japan have been added. Reference to Appendix 7 for country-specific requirements in Japan was provided wherever applicable.	Regulatory Authority (PMDA) request
10.14 Appendix 14 Abbreviations	The abbreviations list has been updated	Changes made for clarification
Throughout the document	Minor editorial corrections and document formatting revisions were made.	Changes made for consistency and clarity, and to comply with company standards.

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