

CLINICAL TRIAL PROTOCOL

Protocol title:	A Phase 1/2, dose escalation, dose expansion, and dose optimization study of the safety, tolerability, and anti-tumor activity of SAR444881 administered alone and in combination with pembrolizumab, cetuximab, and/or chemotherapy in participants with advanced solid tumors
Protocol number:	TCD17465 (formerly BND-22-001)
Amendment number:	13
Compound number (INN/Trademark):	SAR444881 (formerly BND-22) Not applicable
Brief title:	Study of SAR444881 administered alone and in combination with other therapeutics in participants with advanced solid tumors
Acronym:	Not applicable
Study phase:	Phase 1/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	The study centers, the Investigators at each center, and the Coordinating Investigator(s) are listed in a separate document
Regulatory agency identifier number(s):	
IND:	145335
EU Trial Number:	2023-504937-30
NCT:	NCT04717375
WHO:	Not applicable
EUDAMED:	Not applicable
Other:	Not applicable

Date: 13-May-2024

Total number of pages: 275

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Version 9 [Amendment 13]	13-May-2024	To address request for information questions from EU Health Authorities under Clinical Trial Regulation. Revisions include modification of inclusion/exclusion criteria to include specific treatments for determining potential participants for whom all standard of care therapies have failed and no therapies known to provide clinical benefit are available, addition of RET mutation among the known driver alterations, changed requirements for tumor biopsy to state that low risk biopsies are mandatory, medium risk biopsies are optional, and high risk biopsies are prohibited based on the trial objectives and added instruction that biopsy should be performed using ultrasound guidance if imaging is required. Also added clarification that infusion-related reactions may include cytokine release syndrome. As requested, side effects information in the protocol has been updated.
Protocol Version 8 [Amendment 12]	10-Apr-2024	To correct Section 5.2 to state that up to 40-60 participants will be enrolled for the single dose expansion cohort in Sub-Part 2B based on the criteria outlined in Section 5.1. Also, to state that low risk biopsies are mandatory, medium risk biopsies are optional, and high risk biopsies are prohibited based on the trial objectives.
Protocol Version 7 [Amendment 11]	05-Jan-2024	Primary reason for this revised protocol is to modify Sub-Part 2A by removing Cohort A2 (SAR444881 + pembrolizumab combination treatment in 2/3L NSCLC) and replacing it with Cohort E1 (SAR444881 + cetuximab combination treatment in 2L+ NSCLC) based on results from the dose escalation part of the study. Also, in Study Sub-Part 2B, cholangiocarcinoma has been selected as the target disease for Cohort D1 and the selected dose for SAR444881 monotherapy in this cohort is 10 mg/kg Q2W. Other revisions include modification of inclusion criteria to limit the number of cetuximab naive participants enrolled, addition of vital sign monitoring for carboplatin and pemetrexed infusions, clarification that PK and PD sampling will cease when sufficient data are deemed to have been accrued, and appendices added to fulfil EU CTR requirements.
Protocol Version 6.1 [Amendment 10]	20-Dec-2023	To address questions from UK Regulatory Authorities grounds for non approval (GNA) to explicitly state that Cohort A1 patients remain eligible to receive standard approved therapy and to ensure that exclusion of patients with history of clinically significant hypomagnesemia, hypocalcemia, or hypokalemia related to prior cetuximab or other anti-EGFR antibodies applies to Part 2, Cohort C1 as well as Sub-Part 1C.

Protocol Version 6 [Amendment 10]	17-Aug-2023	Primary reason for this revised protocol is the addition of cohorts for Part 2 (Dose Optimization/Expansion phase) evaluating SAR444881 monotherapy and in combination with pembrolizumab, with cetuximab, or pembrolizumab and chemotherapy (carboplatin/pemetrexed), specifically, Part 2 has been divided into two subparts: Sub-Part 2A (Dose Optimization), where the preliminary anti-tumor activity and optimal dose of SAR444881 is assessed in combination with various anti-tumor agents; and Sub-Part 2B (Dose Expansion), where the preliminary anti-tumor activity of SAR444881 is assessed as a monotherapy. Other revisions include modification of the second of the 2 primary objectives of Part 1 to determine the recommended dose(s) of SAR444881, addition of an exploratory objective to explore the effect of SAR444881 [REDACTED] for Part 2, add inclusion criteria specific to each of the Part 2 cohorts and tumor biopsy requirements for Part 2, reclassify exclusion for antibiotic use under Prior/Concomitant Therapy, add exclusion criteria for certain tumor types for specified Part 2 cohorts, add collection of PK parameters for combination agents in Part 2, include dosing regimens for duration of treatment cycle for Part 2, specify maximum numbers of participants in Part 2, and added carboplatin and pemetrexed as study treatments.
Protocol Version 5.2 [Amendment 9]	13-Jul-2023	Administrative amendment to reflect transfer of sponsorship from Biond Biologics to Sanofi. The Biond Biologics study title 'BND-22-001' has been replaced by the Sanofi designation 'TCD17465', and the Biond Biologics drug code, 'BND-22' has been replaced by the Sanofi product code 'SAR444881'. Finally, the sponsor name throughout the document has been changed to Sanofi
Protocol Version 5.1 [Amendment 8]	16-Nov-2022	To address feedback from Regulatory Authorities. Part 1 of the protocol was updated to include monotherapy and combination dose optimization cohorts evaluating activity and safety of more than one BND-22 dose level, to be conducted following completion of dose escalation in Sub-Parts 1A, 1B and 1C. Other revisions include updates reflecting the Sponsor's intention to submit a future protocol amendment with the design of the dose optimization cohorts following evaluation of safety, pharmacodynamic, pharmacokinetic, and preliminary efficacy data from dose escalation cohorts and updates reflecting that the RP2D will be established based on data from dose escalation and added dose optimization cohorts.
Protocol Version 5 [Amendment 7]	14-Aug-2022	Primary reason for this revised protocol is the addition of a BND-22 dose level (20 mg/kg) to be evaluated in the dose escalation phase of the study. Other revisions include addition of rationale for selection of highest BND-22 dose in the dose escalation phase, updating the estimated study duration, and clarifications of the duration of Sub-Part 1B cycles, enrollment of additional participants into BND-22 dose level cohorts of 1 mg/kg and above, requirement for end of treatment (EOT) visit, enrollment without the need for a pre-treatment biopsy, timing of pre-treatment biopsy, time window for completing cetuximab infusions, guidance on collection of PK samples, guidance for management of drug-related infusion reactions in participants treated with study drug combinations, thyroid function tests to be performed, and time window for performing end-of-infusion ECG.

Protocol Version 4.1 [Amendment 6]	16-Aug-2021	To address feedback from Regulatory Authorities. Protocol revisions include updates in thyroid function tests' collection schedule in participants administered BND-22 in combination with pembrolizumab, period of adverse events collection after last dose of study drug(s) and requiring a protocol amendment prior to investigating BND-22 doses higher than 10 mg/kg.
Protocol Version 4 [Amendment 5]	17-June-2021	Primary reason for this revised protocol is the addition of cohorts to Part 1 (Dose Escalation phase) evaluating BND-22 in combination with pembrolizumab or with cetuximab. Other revisions include requirement for previous pembrolizumab treatment in participants with MSI-H/dMMR or TMB-H tumors, shortening the reporting period of non-treatment related adverse events, updated immune-mediated adverse events management algorithms, possibility of adding dose escalation cohorts, requirement to notify Sponsor of adverse events meeting DLT definition, permitting the use of prophylaxis treatment for cetuximab-related dermatologic toxicity, and logistical and administrative changes clarifying specific sections of the protocol.
Protocol Version 3 [Amendment 4]	25-Jan-2021	Logistical and administrative changes clarifying specific sections of the protocol.
Protocol Version 2.2 [Amendment 3]	14-Jan-2021	To address feedback from Regulatory Authorities. Protocol revisions include changes in BND-22 administration instructions and duration of infusion of BND-22 0.1 mg/kg dosage.
Protocol Version 2.1 [Amendment 2]	10-Jan-2021	To address feedback from Regulatory Authorities. Protocol revisions include addition of intense PK sampling at BND-22 steady state to the dose escalation phase (Part 1).
Protocol Version 2 [Amendment 1]	4-Jan-2021	To address feedback from Regulatory Authorities. Protocol revisions include updates to exclusion criteria, addition of stopping rules for safety in Part 2, extending adverse events monitoring to 90 days beyond the last dose of study treatment and extending the duration of contraception after the last dose of BND-22 for women of childbearing potential.
Original Protocol	16-Oct-2020	Not applicable

SUMMARY OF PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

1. OVERALL RATIONALE FOR PROTOCOL VERSION 2 [Amendment 1, 4-January-2021]

The primary reason for this revised protocol is to address feedback from Regulatory Authorities. Protocol revisions include updates to exclusion criteria, addition of stopping rules for safety in the dose expansion phase (Part 2), extending adverse events monitoring from 60 to 90 days beyond the last dose of study treatment and extending the duration of contraception after the last dose of BND-22 for women of childbearing potential.

Text revisions resulting from this amendment are incorporated in the body of Protocol Version 2. Changes to the protocol are summarized below.

1. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.
2. Section 6.2 (Exclusion Criteria): The section was updated so that patients with history of Grade 2 or higher pneumonitis or interstitial lung disease are excluded from the study.
3. Section 6.2 (Exclusion Criteria): The section was updated so that hepatocellular carcinoma (HCC) patients with decompensated cirrhosis (Child Pugh B8 and higher) are excluded from the study.
4. Section 5.1.2.2 (Part 2: BND-22 Cohort Expansion): The section was updated to include stopping rules for safety in the dose expansion phase (Part 2) of the study based on occurrence of a specified number of deaths or treatment emergent life-threatening serious adverse events considered at least possibly related to BND-22.
5. Section 2 (Schedule of Activities), Section 5.1 (Overall Design), Section 5.1.3 (Safety Follow Up Period), Section 10.2.1 (Time Period and Frequency for Collecting AE and SAE Information): The sections were updated to reflect that adverse events are monitored for 90 days beyond the last dose of study treatment.
6. Section 6.1 (Inclusion Criteria), Appendix 4 (Women of Childbearing Potential Definitions and Methods of Contraception): The sections were updated to reflect that the required duration of contraception for women of childbearing potential is the duration of study treatment and 10 months after the last dose of BND-22 (reflecting 5 half-lives of BND-22 plus 6 months after the last dose of study treatment).

2. OVERALL RATIONALE FOR PROTOCOL VERSION 2.1 [Amendment 2, 10-January-2021]

The primary reason for this revised protocol is to address feedback from Regulatory Authorities. Protocol revisions include addition of intense PK sampling at BND-22 steady state to the dose escalation phase (Part 1).

Text revisions resulting from this amendment are incorporated in the body of Protocol Version 2.1. Changes to the protocol are summarized below.

1. Table 10.5-1 (Part 1 (Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule): The table was updated to include additional PK sampling at Cycle 3, Day 1.

3. OVERALL RATIONALE FOR PROTOCOL VERSION 2.2 [Amendment 3, 14-January-2021]

The primary reason for this revised protocol is to address feedback from Regulatory Authorities. Protocol revisions include changes in BND-22 administration instructions and in duration of infusion of BND-22 0.1 mg/kg dosage.

Text revisions resulting from this amendment are incorporated in the body of Protocol Version 2.2. Changes to the protocol are summarized below.

1. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.
2. Section 7.3 (Storage/Preparation/Handling): To address USA FDA request, the section was updated to reflect that BND-22 should be administered within 4 hours of preparation.
3. Section 5.1.2 (Treatment Period), Section 7.4 (Treatments Administered), Table 10.5-1 (Part 1 (Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.5-2 (Part 2 (Dose Expansion) Pharmacokinetic, Immunogenicity and ECG Sampling): To address USA FDA request, the sections were updated to reflect change in duration of infusion of BND-22 0.1 mg/kg dosage level to 30 minutes. This change reflects the intention to administer the 0.1 mg/kg dosage in a concentration similar to the 0.3 mg/kg dosage.

4. OVERALL RATIONALE FOR PROTOCOL VERSION 3 [Amendment 4, 25-January-2021]

The primary reason for this revised protocol is logistical and administrative changes clarifying specific sections of the protocol. Text revisions resulting from this amendment are incorporated in the body of Protocol Version 3. Changes to the protocol are summarized below.

1. Section 2 (SCHEDULE OF ACTIVITIES): “Laboratory Tests” procedure was retitled to clearly indicate which lab tests are to be performed.
2. Table 2-1 (Screening Procedural Outline: Part 1 (Escalation) and Part 2 (Expansion)): The table was updated to clarify that Microsatellite instability (MSI) and/or DNA mismatch repair (MMR) tumor status should be documented if previously tested.
3. Table 10.5-1 (Part 1 (Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.8-1 (Dose Escalation and Expansion (Parts 1 and 2) Biomarker Sampling Schedule): Sample collection time windows were added for 4-, 8- and 24-hour post-infusion sampling.
4. Section 10.8.3 (Tumor Tissue Specimens): The section was updated to reflect that fresh tumor specimens may also be submitted for central laboratory assessment.
5. Section 10.4.5 (Clinical Safety Laboratory Assessments): The section was updated to reflect that laboratory assessments are to be done at the site’s local laboratory.
6. Section 5.1.2.1 (Part 1: BND-22 Dose Escalation), Section 5.1.5 (Safety Review Committee): The sections were updated to reflect that the Safety Review Committee (SRC) may include more than one independent oncology expert member.
7. Section 10.4.3 (Vital Signs): The section was updated to reflect that normal vital signs measured during BND-22 infusions should also be captured in the CRF.
8. Table 10.8-1 (Dose Escalation and Expansion (Parts 1 and 2) Biomarker Sampling Schedule): The table was updated to reflect that C2D15 biomarker blood samples should be collected on the day of BND-22 administration.
9. Abbreviations and Trademarks (Appendix 1): List of abbreviations was updated to be consistent with the body of the protocol.
10. Table 10.5-1 (Part 1 (Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.8-1 (Dose Escalation and Expansion (Parts 1 and 2) Biomarker Sampling Schedule): Annotations were added to the tables clarifying that the duration of infusion of BND-22 0.1 mg/kg dosage is 30 minutes.
11. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.
12. Typographical errors were corrected.

5. OVERALL RATIONALE FOR PROTOCOL VERSION 4 [Amendment 5, 17-June-2021]

The primary reason for this revised protocol is the addition of cohorts in Part 1 of the study (Dose Escalation phase) designed to evaluate the safety and tolerability and determine the RP2D of BND-22 in combination with pembrolizumab or with cetuximab. Changes to the protocol are summarized below.

1. Section 2 (Schedule of Activities), Section 3.1 (Background), Section 3.2 (Study Rationale), Section 4 (Objectives and Endpoints), Section 5.1 (Overall Design), Section 5.2 (Number of Participants), Section 6.1 (Inclusion Criteria), Section 6.2 (Exclusion Criteria), Section 7 (Treatment), Section 8.1 (Discontinuation from Study Treatment), Section 9 (Toxicity and Management), Section 10.1 (Efficacy Assessments), Section 10.2.8 (Immune-mediated Adverse Events), Section 10.4.3 (Vital Signs), Section 10.5 (Pharmacokinetics), Section 10.8 (Biomarkers), Section 11.1 (Sample Size Determination), Section 11.3.3 (Pharmacokinetic Analyses), Appendix 6 (Immune-mediated Adverse Events Management Algorithms): The design of Part 1 (Dose Escalation phase) of the study was updated to include two sub-parts that will evaluate escalating doses of BND-22 in combination with pembrolizumab or with cetuximab.
2. Synopsis: The synopsis was updated to reflect an increase in expected duration of the Dose Escalation phase and to no longer include the number of investigational sites. In addition, sections in the synopsis have been updated to align with protocol revisions.
3. Table 2-1 (Screening Procedural Outline: Part 1 (Escalation) and Part 2 (Expansion)): The table was updated to include documentation of KRAS mutation status for Sub-Part 1C participants with colorectal cancer.
4. Table 2-2 (On Treatment Outline – Sub-Parts 1A/1C: BND-22 Monotherapy/BND-22 in Combination with Cetuximab Dose Escalation), Table 2-3 (On Treatment Outline – Sub-Part 1B: BND-22 in Combination with Pembrolizumab Dose Escalation), Section 7.4 (Treatments Administered): The tables and section were updated to reflect that changes in timing of Cycle 1 visits are allowed after Sponsor approval.
5. Section 5.1.1.1 (Medical History and Demographic Data) – The section was updated to clarify what medical history data should be collected.
6. Section 5.2.1.1 (Part 1: BND-22 Dose Escalation) – The section was updated to reflect that additional cohorts evaluating doses above 10 mg/kg of BND-22 may be added based on emerging PK or pharmacodynamic data suggesting maximal suppression of ILT2 is not being maintained throughout the dosing interval or immune cell activation has not plateaued.
7. Section 6.1 (Inclusion Criteria) – The section was updated to reflect that a missing biopsy due to a participants' decline to undergo the on-treatment biopsy after study drug treatment has started, will not be considered a protocol deviation.
8. Section 6.1 (Inclusion Criteria) – The section was updated to reflect that participants with MSI-H and/or dMMR tumors or TMB-H tumors should have received pembrolizumab or another anti-PD-1 or anti-PD-L1 therapeutic antibody, prior to enrollment into the study.
9. Section 7.2 (Ordering Study Treatment) – The section was updated to clarify the contact details for drug supply requests.

10. Section 7.11 (Permitted Therapy) – The section was updated to reflect that topical and systemic prophylaxis treatment for cetuximab-related dermatologic toxicity is permitted.
11. Section 9.1 (Dose-Limiting Toxicities (DLTs)) – The section was updated to clarify that a DLT will be defined based on the occurrence of drug-related AEs during the 28 days starting with Day 1 of Cycle 1 (rather than during Cycle 1) and to reflect that the Sponsor should be notified of adverse events that meet DLT criteria within 24 hours.
12. Section 10.2.1 (Time Period and Frequency for Collecting AE and SAE Information), Table 2-5 (Safety Follow-Up Procedural Outline for All Study Parts (Escalation and Expansion)) – The section and table were updated to reflect that adverse events unrelated to study drug(s) should be collected until 30 days after last dose of study drug(s).
13. Section 10.4.1 (Electrocardiograms (ECGs)) – The section was updated to clarify that ECGs may be performed after IV-line insertions or blood draws once a reasonable time has passed and the participant is relaxed.
14. Table 10.5-1/2/3/4 (Pharmacokinetic, Immunogenicity and ECG Sampling Schedule) – The tables were updated to clarify that the end-of-infusion timepoint is the time at which the full drug dose was administered, including any drug remaining in the infusion set.
15. Section 10.8.3 (Tumor Tissue Specimens) – The section was updated to reflect a 7 days time window for the on-treatment biopsy.
16. Appendix 3 (Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting) – The appendix was updated to clarify when paper forms should be used for submitting SAE and Pregnancy reports.
17. Appendix 6 (Immune-mediated Adverse Events Management Algorithms) – The appendix was updated to reflect that study drug(s) should be discontinued if immune mediated AEs are not resolved within 12 weeks of initiating steroids or if steroid dose cannot be reduced. In addition, the management algorithms of immune-mediated hepatic adverse reactions were updated to be used based on tumor involvement of the liver rather than a diagnosis of hepatocellular carcinoma.
18. The term “BND-22” was replaced with “study drug(s)” in relevant sections of the protocol to reflect administration of additional investigational products.
19. Typographical errors were corrected.

6. OVERALL RATIONALE FOR PROTOCOL VERSION 4.1 [Amendment 6, 16-August-2021]

The primary reason for this revised protocol is to address feedback from Regulatory Authorities. Protocol revisions include updates in thyroid function tests' collection schedule in participants administered BND-22 in combination with pembrolizumab, period of adverse events collection after last dose of study drug(s) and requiring a protocol amendment prior to investigating BND-22 doses higher than 10 mg/kg.

Changes to the protocol are summarized below.

1. Table 2-3 (On Treatment Outline – Sub-Part 1B: BND-22 in Combination with Pembrolizumab Dose Escalation), Table 2-5 (Safety Follow-Up Procedural Outline for All Study Parts (Escalation and Expansion)): The tables were updated to reflect that in participants administered BND-22 in combination with pembrolizumab, thyroid function tests will be checked on day 1 of all treatment cycles.
2. Section 10.2.1 (Time Period and Frequency for Collecting AE and SAE Information), Table 2-5 (Safety Follow-Up Procedural Outline for All Study Parts (Escalation and Expansion)) – The section and table were updated to reflect that all adverse events, regardless of relationship to study drug(s), will be collected for 90 days after the last dose of BND-22, pembrolizumab or cetuximab.
3. Section 5.1.2.1 (Part 1: BND-22 Dose Escalation): The section was updated to reflect that a protocol amendment would be submitted prior to investigating BND-22 doses higher than 10 mg/kg.
4. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.

7. OVERALL RATIONALE FOR PROTOCOL VERSION 5 [Amendment 7, 14-August-2022]

The primary reason for this revised protocol is the addition of a 20 mg/kg dose level in Part 1 (Dose Escalation phase) of the study.

Changes to the protocol are summarized below.

1. Section 5.1 (Overall Design), Section 5.1.2.1 (Part 1: BND-22 Dose Escalation), Section 5.2 (Number of Participants), Section 7.4 (Treatments Administered), Section 11.1 (Sample Size Determination), Section 1 (Synopsis): The design of Part 1 of the study (Monotherapy and Combinations Dose Escalation phase) was updated to include an additional BND-22 dose level of 20 mg/kg in all three sub-parts. The number of participants planned to be enrolled into Part 1 and estimated study duration were updated to reflect the addition of a dose level.
2. Section 3.2.7 (Rationale for Dose Selection): The section was updated to include the rational for selection of highest BND-22 dose in the dose escalation phase.
3. Section 5.1 (Overall Design): The section was updated to clarify that the duration of a cycle in Sub-Part 1B is 21 days and that timing of safety follow up visits is relative to study drug(s) discontinuation.
4. Section 5.1.2.1 (Part 1: BND-22 Dose Escalation), Section 11.1 (Sample Size Determination): Phrasing was revised to clarify that participants may be added to all BND-22 dose level cohorts of 1 mg/kg and above once the tolerability of doses has been established. Text regarding the potential addition of BND-22 dose levels higher than 10 mg/kg was deleted.
5. Section 5.1.3 (Safety Follow Up Period): The section was updated to clarify when an on-treatment visit may be considered the end-of-treatment (EOT) visit.
6. Section 6.1 (Inclusion Criteria), Section 10.8.3 (Tumor Tissue Specimens), Table 10.8-1 (Single Agent Dose Escalation and Expansion (Sub-Part 1A and Part 2) Biomarker Sampling Schedule), Table 10.8-2 (BND-22 in Combination with Pembrolizumab Dose Escalation (Sub-Part 1B) Biomarker Sampling Schedule), Table 10.8-3 (BND-22 in Combination with Cetuximab Dose Escalation (Sub-Part 1C) Biomarker Sampling Schedule): The section and tables were updated to clarify enrollment, without the need for a pre-treatment tumor biopsy, of participants with an available archival sample. Text describing collection process of pre-treatment biopsy was corrected.
7. Section 7.4.3 (Cetuximab Treatment): Time window for completing cetuximab infusions was updated.
8. Section 9.4 (Management of Drug-Related Infusion Reactions): The section was updated to clarify the infusion reactions management guidance for participants treated with study drug combinations.
9. Section 10.4.5 (Clinical Safety Laboratory Assessments): The section was updated to clarify that Total T3 may be tested instead of Free T3 dependent on local standards.
10. Section 10.5 (Pharmacokinetics), Table 10.5-1 (Sub-Part 1A (BND-22 Single Agent Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.5-2 (Sub-Part 1B (BND-22 in Combination with Pembrolizumab Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.5-3 (Sub-Part 1C (BND-22 in Combination with Cetuximab Dose Escalation) Pharmacokinetic,

- Immunogenicity and ECG Sampling Schedule), Table 10.5-4 (Part 2 (BND-22 Single Agent Dose Expansion) Pharmacokinetic, Immunogenicity and ECG Sampling): The section and tables were updated to clarify that post infusion PK samples (end-of-infusion, 4 hours, and 8 hours timepoints) should not be collected from the same IV access as drug was administered.
11. Table 10.5-1 (Sub-Part 1A (BND-22 Single Agent Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.5-2 (Sub-Part 1B (BND-22 in Combination with Pembrolizumab Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.5-3 (Sub-Part 1C (BND-22 in Combination with Cetuximab Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule), Table 10.5-4 (Part 2 (BND-22 Single Agent Dose Expansion) Pharmacokinetic, Immunogenicity and ECG Sampling): The tables were updated to reflect that an ECG should be performed in the end of treatment visit and to clarify the time window for performing end-of-infusion ECGs.
 12. Section 10.8.3 (Tumor Tissue Specimens): The section was updated to clarify that the pre-treatment biopsy does not need to be collected prior to the Screening period's imaging scan.
 13. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.
 14. Typographical errors were corrected.

8. OVERALL RATIONALE FOR PROTOCOL VERSION 5.1 [Amendment 8, 16-November-2022]

The primary reason for this revised protocol is to address feedback from Regulatory Authorities. Protocol revisions include the addition of Part 1 monotherapy and combination cohorts evaluating activity and safety of more than one BND-22 dose level, to be conducted following completion of dose escalation in Sub-Parts 1A, 1B and 1C. The design of the added dose optimization cohorts will be included in a future protocol amendment following evaluation of safety, pharmacodynamic, pharmacokinetic, and preliminary efficacy data from dose escalation cohorts.

Changes to the protocol are summarized below.

1. Section 3.2.6 (Study Design Rationale), Section 3.2.7 (Rationale for Dose Selection (BND-22 Expansion Phase Dose)), Section 5.1 (Overall Design), Section 5.1.2.1 (Part 1: BND-22 Dose Escalation), Section 5.1.2.1 (Determining the Recommended Phase 2 Dose (RP2D)), Section 5.1.2.2 (Part 2: BND-22 Cohort Expansion): The sections were updated to reflect the addition of Part 1 dose optimization cohorts, evaluating more than one BND-22 dose level, to be conducted following completion of dose escalation cohorts and prior to the determination of the RP2D. Design of the added dose optimization cohorts will be included in a future protocol amendment following evaluation of safety, pharmacodynamic, pharmacokinetic, and preliminary efficacy data from dose escalation cohorts.
2. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.

9. OVERALL RATIONALE FOR PROTOCOL VERSION 5.2 [Amendment 9, 13-July-2023]

The primary reason for this administrative amendment is to reflect transfer of sponsorship from Biond Biologics to Sanofi.

Changes to the protocol are summarized below.

1. The Biond Biologics study title ‘BND-22-001’ has been replaced by the Sanofi designation ‘TCD17465’.
2. The Biond Biologics drug code, ‘BND-22’ has been replaced by the Sanofi product code ‘SAR444881’.
3. The sponsor name throughout the document has been changed to Sanofi.
4. Section 7.3 (Storage/Preparation/Handling) updated to reflect new stability data for SAR444881

10. OVERALL RATIONALE FOR PROTOCOL VERSION 6 [Amendment 10, 17-Aug-2023]

This amended protocol (amendment 10) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

The primary reason for this revised protocol is the addition of cohorts for Part 2 (previously named Dose Expansion phase, renamed as 'Dose Optimization/Expansion' phase owing to revision of study design) evaluating SAR444881 monotherapy and in combination with pembrolizumab, with cetuximab, or pembrolizumab and chemotherapy (carboplatin/pemetrexed). Specifically, Part 2 has been divided into two subparts: Sub-Part 2A (Dose Optimization), where the preliminary anti-tumor activity and optimal dose of SAR444881 is assessed in combination with various anti-tumor agents; and Sub-Part 2B (Dose Expansion), where the preliminary anti-tumor activity of SAR444881 is assessed as a monotherapy. Protocol revisions include modification of the second of the 2 primary objectives of Part 1 to determine the recommended dose(s) of SAR444881, addition of a second primary objective of Part 2 to define the optimal dose of SAR444881, [REDACTED] add Sanofi product code (SAR444881) and study number (TCD17465) to the protocol, add inclusion criteria specific to each of the Part 2 cohorts and tumor biopsy requirements for Part 2, reclassify exclusion for antibiotic use under Prior/Concomitant Therapy, add exclusion criteria for certain tumor types for specified Part 2 cohorts, add collection of PK parameters for combination agents in Part 2, include dosing regimens for length of treatment cycle for Part 2, specify maximum numbers of participants in Part 2, and add carboplatin and pemetrexed as study treatments.

Changes to the protocol are summarized below.

1. Title/ cover page of the document and in Section 1 (SYNOPSIS): Title of study was revised to include dose optimization and chemotherapy and to align with brief title.
2. Table 2-4 (On-Treatment Procedural Outline - Part 2: SAR444881 Dose Optimization/Expansion Cohorts C1 and D1) was renamed and updated to cover Cohorts C1 and D1; cetuximab administration was added, for Cohort C1 only; notes for thyroid function texts were revised; old text "dose expansion" is replaced by "dose optimization/expansion" [REDACTED] Assessments were also added; a new Table 2-5 (On-Treatment Procedural Outline Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1, A2, and B1) was added; and Table 2-6 (Safety Follow-Up Procedural Outline for All Study Parts [Escalation and Optimization/Expansion]) was renumbered, renamed and updated to include [REDACTED] Assessments.
3. Section 3.2.3.1 (SAR444881 in Combination with Pembrolizumab) was expanded with added information on pembrolizumab pharmaceutical and therapeutic background and pre-clinical and clinical trials.
4. Section 3.2.6 (Study Design Rationale): The term "expansion" (e.g., expansion phase, expansion study, etc.) has been replaced by "optimization/expansion". Earlier combination with only pembrolizumab or cetuximab is revised to combination with pembrolizumab or cetuximab and/or chemotherapy with pemetrexed and carboplatin. The primary objective of Part 2 was changed to include determination of the recommended dose(s) for SAR444881 as monotherapy and in combination with pembrolizumab and/or cetuximab; text related to interim analysis and futility study was deleted. Colorectal cancer was added as a tumor type

- of focus in Part 2. Bayesian toxicity monitoring on DLT was added for all optimization/expansion cohorts.
5. Section 3.2.7 (Rationale for Dose Selection): RP2D was replaced with determination of recommended dose(s) for optimization/expansion. The paragraph with heading "SAR444881 Escalation Phase Highest Dose" has been deleted and the sentence "The dose of SAR444881 is planned to be escalated up to 20 mg/kg" has been newly added.
 6. Section 3.2.8.5 (SAR444881 in Combination with Pembrolizumab and chemotherapy) was added and the subsequent section was renumbered.
 7. Section 3.2.8.6 (Benefit/Risk Assessment): Statement of acceptable benefit-risk balance was expanded to include combination of SAR444881 with pembrolizumab and chemotherapy regimens (carboplatin, pemetrexed).
 8. Section 4 (OBJECTIVES AND ENDPOINTS): Section was revised to include modification of the second of the 2 primary objectives of Part 1 to determine the recommended dose(s) of SAR444881. Table 4-2 Objectives and Endpoints: Optimization/Expansion (Part 2) was renamed and revised accordingly; primary endpoint wording was modified to allow other datapoints to supplement ORR, secondary endpoint wording was modified to add disease control rate and to clarify definition of duration of response; [REDACTED], with accompanying endpoint.
 9. Section 5.1 (Overall Design): Description of Part 2, composed of Sub-Part 2A for dose optimization and Sub-Part 2B for dose expansion, was added. Figure 5.1 (A schema of the proposed study) was replaced and Figure 5.2 (Overall design for dose optimization/expansion), Figure 5.3 (Schematic for study periods and participant flow for Cohorts C1 and D1) and Figure 5.4 (Schematic for study periods and participant flow for Cohorts A1, A2, and B1) were added. Paragraph on a future protocol amendment to include design of the dose optimization cohorts was removed and Part 2 description was revised.
 10. Section 5.1.2 (Treatment Period): Dosing of SAR444881 in combination with pembrolizumab, cetuximab, carboplatin, and pemetrexed was added. Dosing sequence for Dose Optimization Cohort A1 was added.
 11. Section 5.1.2.1 (Part 1: SAR444881 Dose Escalation): Paragraph on a future protocol amendment to include design of the dose optimization cohorts was removed; sub-section heading "Determining the Recommended Phase 2 Dose (RP2D)" was updated to "Determining the Recommended Dose(s) for Dose Optimization/Expansion" and the text was updated accordingly.
 12. Section 5.1.2.2 (Part 2: SAR444881 Cohort Expansion): Section was renamed Part 2: SAR444881 Cohort Optimization/Expansion and text was updated accordingly.
 13. Section 5.1.2.3 (Safety Run-In [Cohort A1]) was added.
 14. Section 5.1.5 (Safety Review Committee): Update to reflect continuation of Safety Review Committee into Part 2.
 15. Section 5.2 (Number of Participants): Enrollment limit of total number of participants was increased from 258 to 456 participants. Additional number of participants were added for Part 2.
 16. Section 5.3 (End of Study Definition): For Part 2, data cut-off for primary analysis per cohort and for the study were defined.

17. Section 6.1 (Inclusion Criteria): For Part 2, inclusion criteria for each of the 5 cohorts were added with respect to tumor type. Mandatory biopsy requirements for participants in all dose optimization/expansion cohorts are given.
18. Section 6.2 (Exclusion Criteria): Exclusion for antibiotic use or uncontrolled infection was added. Additional exclusions for Sub-Part 2A Cohorts A1, A2, and C1 were added.
19. Section 7 (Treatment): Carboplatin and pemetrexed were added as investigational medicinal products for this study.
20. Table 7-1 (Study Treatments for TCD17465): Carboplatin, pemetrexed, diphenhydramine, folic acid, vitamin b12 and dexamethasone were added. Product Description / Class and Dosage Form, Potency, packaging and storage conditions were updated. The text "Non-IMP" has been replaced with "AxMP".
21. Table 7.1-1 (Selection and Timing of Dose): Clarified dose selection of SAR444881 and frequency of administration for cohorts in Part 2, added carboplatin and pemetrexed as study treatments, and added premedication details.
22. Section 7.4.4 (Pemetrexed Treatment) and Section 7.4.4.1 (Pemetrexed Premedication): Sections were added, including reference to MASCC guidelines for prophylaxis with dexamethasone.
23. Section 7.4.5 (Carboplatin Treatment): Section was added.
24. Section 7.6.1 (Dosage Modification for Chemotherapy): Section was added, including Table 7.5-1 (Dose modification for chemotherapy agents), Table 7.5-2 (Recommended dose modifications for chemotherapy hematological toxicity), and Table 7.5-3 (Recommended dose modifications for chemotherapy non-hematological toxicity). Subsequent sections were renumbered.
25. Section 7.6.2 (Method of Treatment Assignment): Part 2 (optimization/expansion cohorts) details were added.
26. Section 7.6.3 (Participant Numbering): Part 2 (optimization/expansion cohorts) details were added.
27. Section 7.7 (Blinding): Part 2 (optimization/expansion cohorts) details were added.
28. Section 7.10.1 (Prohibited and/or Restricted Treatments): List was revised.
29. Section 9.2.1 (Withholding SAR444881 and Pembrolizumab Doses): Reference to Table 9.3-1 for dose modification and adverse events related to pembrolizumab was added.
30. Section 9.2.3 (Withholding Carboplatin and Pemetrexed Doses): Section was added.
31. Section 9.3 (Management Algorithms for Immuno-Oncology Agents): Section was modified and new information related to immune-related adverse events associated with pembrolizumab and SAR444881 was added.
32. Table 9.3-1 (Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444881): Table was added.
33. Section 9.4.1 (Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab): Section was added, including Table 9.4.1-1 (Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines).
34. Section 10.1.2 [REDACTED]: Section was added,

- including reference to literature and Appendix 8, which contains a copy of the [REDACTED] instrument.
35. Section 10.2.3 (Follow-up of AEs and SAEs): Section has been split into Part 1 (Dose Escalation) and Part 2 (Dose Optimization/Expansion) and renumbered as Section 10.2.2.1 and Section 10.2.2.2 and following sections have been renumbered.
 36. Section 10.2.3 (Regulatory Reporting Requirements for SAEs): Basis for reporting requirement has been updated to reflect update in EU regulations.
 37. Section 10.3 (Overdose, Medication Errors, Misuses or Abuses of Medicinal Product): Section name has been modified and text has been updated.
 38. Section 10.4 (Events of Clinical Interest (ECI; Part 2 only): Section has been added and subsequent sections are renumbered.
 39. Section 10.5.1 (Electrocardiograms [ECGs] and Left Ventricular Ejection Fraction [LVEF]): Section name was modified. LVEF and troponin were added, to be measured in Part 2 only.
 40. Section 10.5 (Pharmacokinetics): Section was renumbered to 10.6 and collection of serum samples for pembrolizumab and cetuximab was added.
 41. Section 10.6 (Immunogenicity): Section was renumbered to 10.7 and updated to include rationale for not assessing immunogenicity of the combination products pembrolizumab and cetuximab. Table 10.5-4 (Part 2 [SAR444881 Dose Optimization Cohort C1 and Dose Expansion Cohort D1] Pharmacokinetic, Immunogenicity and ECG Sampling) was renamed and revised and Table 10.5-5 (Part 2 [SAR444881 Dose Optimization Cohorts A1, A2, and B1] Pharmacokinetic, Immunogenicity and ECG Sampling) was added.
 42. Table 10.8-4 (Dose Optimization/Expansion [Part 2] Biomarker Sampling Schedule): Table was added.
 43. Section 10.8.1 (Rationale for Evaluation of Pharmacodynamic and Potential Predictive Biomarkers): Membrane HLA G expression in tumor cells was removed from the list of biomarkers named to be analyzed in the study (but list is not limiting).
 44. Section 10.8.2.3 (Circulating tumor DNA [ctDNA]): Section was added.
 45. Section 10.8.2.4 (Genomics and Transcriptomics): Section was added.
 46. Section 10.8.3.2 (Gene Expression Profiling): Specification of methods was removed since the examinations themselves may or may not be conducted.
 47. Section 10.8.3.3 (Characterization of Tumor Biomarkers): Circulating tumor DNA (ctDNA) was added to the list of named biomarkers that may be assessed in the study (but list is not limiting).
 48. Section 10.8.4 (Additional Research Collection): Section was removed and replaced by section titled Use of Biological Samples and Data for Future Research.
 49. Section 10.9 ([REDACTED] Assessments): Section was added, including Table 10.9-1 ([REDACTED] assessment and estimated response time by dose optimization/expansion cohort).
 50. Section 11.1.2 (Dose Optimization/Expansion): Section on statistical analysis of Part 2 was revised, including replacement with a new Table 11.1-1 (Estimated objective response rate [ORR] and 95% CI).
 51. Section 11.2 (Populations for Analyses): Intention to treat (ITT) population definition was added.

52. Section 11.3.6 (Other Analyses): Analyses on [REDACTED] data will be described in a dedicated [REDACTED] SAP.
53. Section 11.3.7 (Interim Analyses): Section was revised, including addition of Table 11.3.7-1 (Bayesian toxicity monitoring plan in dose optimization/expansion phase).
54. Appendix 1 (Abbreviations and Trademarks): Some abbreviations have been modified or added.
55. Appendix 2 (Study Governance Considerations): Section has been updated to reflect requirements of Regulation No 536/2014 of the European Parliament and the Council of the European Union and disclosure of information about clinical trials and results.
56. Appendix 6 (Immune-mediated Adverse Events Management Algorithms): Appendix was renamed SAR444881-related immune-mediated Adverse Events Management Algorithms.
57. Appendix 8 ([REDACTED]): A copy of the [REDACTED] [REDACTED] was added.
58. Appendix 9 (Two-Stage Design): Section was added.
59. Section 13 (REFERENCES): New references were added.
60. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.
61. Typographical errors were corrected, and formatting and editorial changes were made throughout the document.

11. OVERALL RATIONALE FOR PROTOCOL VERSION 6.1 [Amendment 10, 20-Dec-2023]

This amended protocol (amendment 10) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

Changes to the protocol are summarized below.

1. Section 6.1 (Inclusion Criteria): Inclusion criterion 2a was updated to explicitly state that patients enrolled into Cohort A1 remain eligible to receive standard approved therapy.
2. Section 6.2 (Exclusion Criteria): Exclusion criterion 1m was modified to ensure that exclusion of patients with history of clinically significant hypomagnesemia, hypocalcemia, or hypokalemia related to prior cetuximab or other anti-EGFR antibodies applies to Part 2, Cohort C1 as well as Sub-Part 1C.
3. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.

12. OVERALL RATIONALE FOR PROTOCOL VERSION 7 [Amendment 11, 05-Jan-2024]

This amended protocol (amendment 11) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

The primary reason for this revised protocol is to modify Sub-Part 2A by removing Cohort A2 (SAR444881 + pembrolizumab combination treatment in 2L+ NSCLC) and replacing it with Cohort E1 (SAR444881 + cetuximab combination treatment in 2L+ NSCLC) based on results from the dose escalation part of the study. Also, in Study Sub-Part 2B, cholangiocarcinoma has been selected as the target disease for Cohort D1.

Changes to the protocol are summarized below.

1. Figure 1 (Study Design Schematic): Updated to reflect selection of cholangiocarcinoma as the indication to be treated in Cohort D1.
2. Table 1-1 (Overview of study cohorts): Updated to remove Cohort A2 and add Cohort E1, to expand intervention in Cohort C1 to include treatment as second line intervention and to reflect selection of cholangiocarcinoma as the indication to be treated in Cohort D1.
3. Table 2-1 (Screening Procedural Outline: Part 1 [Escalation]) and Part 2 [Optimization/Expansion]): Window of 72 hours was given for Day 1 physical measurements. End of treatment biopsies were limited to Part 1 participants.
4. Table 2-4 (On Treatment Procedural Outline: Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1, and E1): Title was changed to add Cohort E1. Added that reflex testing (free T3 and free T4) is conducted if TSH is abnormal. Removed optional end of treatment biopsy, which was included in table in error. Added Cohort E1 to [REDACTED] assessment. Added Cohort E1 to cetuximab administration. Added footnote that on-treatment biopsy is required for at least 20 total participants in all dose optimization/expansion cohorts, if clinically feasible.
5. Table 2-5 (On-Treatment Procedural Outline: Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1): Title was changed to remove Cohort A2. Reference to Table 10.5-5 was added for ECGs. Removed optional end of treatment biopsy, which was included in table in error. Corrected cycle length to 21 days for Cohorts A1 and B1 where needed. Corrected reference from Table 10.5-4 to Table 10.5-5 for PK and immunogenicity/ADA sampling. Added footnote that on-treatment biopsy is required for at least 20 total participants in all dose optimization/expansion cohorts, if clinically feasible.
6. Section 3.2.3.2 (SAR444881 in Combination with Cetuximab): Added justification for study of SAR444881 + cetuximab combination in NSCLC.
7. Section 3.2.4 (Clinical Experience): Section updated with information from this study as of 30 April 2023.
8. Section 3.2.7 (Rationale for Dose Selection): Added new subsection for SAR444881 Doses for Dose Optimization/Expansion. Table 3-1 - Per Cohort SAR444881 Dose Levels for Dose Optimization (Part 2, Stage 1) was added.
9. Section 3.2.8 (Anticipated Risks): Added reference to Section 3.2.4 (Clinical Experience) for limited human safety data available from this ongoing study.

10. Section 3.2.8.2 (Pembrolizumab): Reference for additional safety information was updated from the SAR444881 IB to the country-approved product labeling.
11. Section 3.2.8.3 (Cetuximab): Reference to additional safety information was changed to the country-approved product labeling.
12. Figure 5.2 (Overall design for dose optimization/expansion): Figure was updated to remove Cohort A2 and add Cohort E1 and add target disease cholangiocarcinoma in Cohort D1.
13. Table 5.1-1 (Overview of study cohorts) was updated to remove Cohort A2 and add Cohort E1 and add target disease cholangiocarcinoma in Cohort D1.
14. Section 5.1 (Overall Design): Indication for Cohort D1 was specified as cholangiocarcinoma. Flexibility for randomization of Stage 2 of the study was added and design may include a single dose level based on emerging data from Stage 1.
15. Figure 5.3 (Schematic for study periods and participant flow for Part 2 Cohorts C1, D1, and E1): Title was updated and Cohort E1 was included.
16. Figure 5.4 (Schematic for study periods and participant flow for Part 2 Cohorts A1 and B1): Title was updated and Cohort A2 was removed.
17. Section 5.1.2.2 (Part 2: SAR444881 Dose Optimization/Expansion): Reference added to Section 3.2.7 for the doses chosen for dose optimization (Part 2, Stage 1).
18. Section 5.1.2.3 (Safety Run-In [Cohort A1]): The initial SAR444881 dose to be tested in the safety run-in for Cohort A1 was set to 10 mg/kg.
19. Section 6.1 (Inclusion Criteria): Inclusion criteria for Cohort A2 were deleted. Inclusion criteria for Cohort C1 were updated to specify participants with RAS-mutant and BRAF-mutant colorectal cancer are eligible for enrollment and prior anticancer therapy requirements were made less restrictive. Criteria for Cohort E1 were added. Inclusion criteria for Cohort D1 were aligned to the selected test indication, cholangiocarcinoma. Physical and laboratory findings criteria were updated.
20. Section 6.2 (Exclusion Criteria): Medical history requirements were updated for Cohorts A1 and B1 and C1 and E1. Cohort A2 was removed and Cohort E1 was added under restriction for radiation therapy. Exclusion for participants with a history of (non-infectious) pneumonitis /interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease was removed.
21. Table 7-1 (Study Treatments for TCD17465): Potency of cetuximab applicable for use in Canada was specified to include 200 mg/100 mL.
22. Table 7.1-1 (Selection and Timing of Dose): Dose of SAR444881 was specified for Part 2 cohorts. Frequency of administration of SAR444881 was specified for Cohort E1 and Cohort A2 was removed. Cohort E1 was added to dosing schedule for cetuximab.
23. Section 7.4 (Treatments Administered): Cohort A2 was removed and Cohort E1 was added.
24. Section 7.4.1 (SAR444881 Treatment): Instruction was changed for resumption of study therapy for eligible participants.
25. Section 7.4.3 (Cetuximab Treatment): Added justification for dose used in NSCLC.
26. Section 8.1 (Discontinuation from Study Treatment): Cohort A2 was removed and Cohort E1 was added.

27. Section 10.4 (Adverse Events of Special Interest [AESI; Part 2 only]): Section heading changed from Events of Clinical Interest (ECI; Part 2 only).
28. Section 10.5.3 (Vital Signs): Specifications for monitoring vital signs during pemetrexed and carboplatin infusions were added.
29. Section 10.5.4 (Tumor Tissue Specimens): Cohort A2 was removed and Cohort E1 was added.
30. Table 10.4.5-1 (Clinical Laboratory Assessments): Cohort A2 was removed and Cohort E1 was added.
31. Table 10.5-4 (Part 2 [SAR444881 Dose Optimization Cohort C1 and E1 and Dose Expansion Cohort D1] Pharmacokinetic, Immunogenicity and ECG Sampling): Cohort E1 was added. ECG-12 Lead at C1D15, C2D15, C3D1, and Cycle X Day 1 Predose was removed. Footnote was added to stipulate that SAR444881 pre-dose PK samples are to be taken prior to cetuximab infusion and separate pre-dose PK samples are to be taken for cetuximab and SAR444881.
32. Table 10.5-5 (Part 2 [SAR444881 Dose Optimization Cohorts A1 and B1] Pharmacokinetic, Immunogenicity and ECG Sampling): Cohort A2 was removed. ECG-12 Lead at C3D1 and Cycle X Day 1 Predose was removed. Footnote was added to stipulate that separate pre-dose PK samples are to be taken for pembrolizumab and SAR444881.
33. Table 10.8-1 (Single Agent Dose Escalation [Sub-Part 1A] Biomarker Sampling Schedule), Table 10.8-2 (SAR444881 in Combination with Pembrolizumab Dose Escalation [Sub-Part 1B] Biomarker Sampling Schedule), and Table 10.8-3 (SAR444881 in Combination with Cetuximab Dose Escalation [Sub-Part 1C] Biomarker Sampling Schedule): Footnote was updated to stipulate that sampling may be discontinued once sufficient data have been collected.
34. Table 10.8-4 (Dose Optimization/Expansion [Part 2] Biomarker Sampling Schedule): Cohort A2 was removed and Cohort E1 was added. Footnote was updated to stipulate that pre-dose samples will be taken prior to pembrolizumab administration for Cohorts A1 and B1, prior to cetuximab administration for Cohorts C1 and E1, and prior to SAR444881 for Cohort D1. Footnote was added to provide a window of ± 4 hours for biomarker sampling at C1D1 4:00 hours and C1D2 24:00 hours.
35. Table 10.9-1 (██████ assessment and estimated response time by dose optimization/expansion cohort): Cohort A2 was removed and Cohort E1 was added.
36. Table 11.3.3-1 (Pharmacokinetic Endpoints and Analyses): Scatter plots vs dose for each cycle measured (C_{trough}) was added.
37. Section 12 (Appendix 2 – Study Governance Considerations): Good Clinical Practice section was expanded to include Investigators' responsibility to provide oversight of the conduct of the study at the site. Study/Site Termination section was added.
38. Section 12 (Appendix 3 - Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting): Definition of Adverse Events has been expanded to comply with EU Clinical Trial Regulation (CTR).
39. Section 12 (Appendix 9 – Two-Stage Design): In Table APP-9-1 – Reference and target ORRs for each indication, combination therapy for NSCLC was changed to SAR444881 + cetuximab as 2 L and later therapy.

40. Section 12 (Appendix 10 – Country-Specific/Region Requirements): Appendix was added to include information required by Germany, France, and EU.
41. Section 12 (Appendix 11 – Contingency Measure for a Regional or National Emergency that is Declared by a Governmental Agency): Appendix was added to include information pertaining to Germany.
42. Section 12 (Appendix 12 – Collection, Storage and Future Use of Data and Human Biological Samples): Appendix was added to note availability of a separate appendix to comply with EU Clinical Trial Regulation (CTR).
43. Section 13 (REFERENCES): New references were added.
44. Synopsis: Sections in the synopsis have been updated to align with protocol revisions. In addition, Secondary Objectives for Dose Optimization/Expansion (Part 2) were updated to specify examples of the additional parameters of anti-tumor activity of SAR444881 provided in Section 4, Table 4-2.
45. Typographical errors were corrected, and formatting and editorial changes were made throughout the document.

12. OVERALL RATIONALE FOR PROTOCOL VERSION 9 [Amendment 13, 13-May-2024]

This amended protocol (amendment 13) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

The primary reason for this revised protocol is to address requests for information from EU Health Authorities under Clinical Trial Regulation to allow expansion of the study to sites within the European Union. Only changes required for compliance to the EU request for information are included in this amended protocol.

Changes to the protocol are summarized below.

1. Table 2-4 (On Treatment Procedural Outline - Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1 and E1) and Table 2-5 (On-Treatment Procedural Outline - Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1): Description of low, moderate, and high risk lesion biopsies was added to footnote c.
2. Section 3.2.4 (Clinical Experience): Section updated with safety information from this study as of 14 January 2024.
3. Section 3.2.8.1 (SAR444881): Clarification that infusion-related reactions (IRR) may include cytokine release syndrome (CRS) was added.
4. Section 6.1 (Inclusion Criteria): Inclusion criterion 1 regarding Signed Written Informed Consent was revised to require that going forward in Part 2, participants with low risk biopsies must consent to and undergo mandatory pre- and on-treatment biopsies. Also specified that moderate risk biopsies are optional, not mandatory (Part 2 only) and high risk biopsies are not acceptable in this trial. Inclusion criterion for Sub-Part 2A (SAR444881 Dose Optimization for Cohort C1) was updated to state that patients with RAS wild type colorectal cancer, RAS-mutant colorectal cancer, and BRAF-mutant colorectal cancer are eligible for enrollment and should have either failed or relapsed on or be ineligible for appropriate specified treatments. Inclusion criterion for Cohort E1 was updated to include RET mutation among the known driver alterations and to specify that participants with driver mutations must have failed or relapsed on or be ineligible for available targeted therapies. Inclusion criterion for Sub-Part 2B (SAR444881 Dose Expansion Cohort D1) was updated to add that participants must have failed all standard of care therapies. Inclusion criterion 4.2 regarding Tumor biopsies for Dose Optimization/Expansion was also revised to specify that baseline biopsy was mandatory for participants in all dose optimization/expansion cohorts with low risk biopsies. Moderate risk biopsies were made optional and high risk biopsies were clarified as being not acceptable in this trial. Added instruction that if imaging is required to obtain biopsy material, the biopsy should be performed using ultrasound guidance to prevent additional study-related radiation dose. The target to have 20 participants in all dose optimization/expansion cohorts with on-treatment biopsy, if clinically feasible, was made non-mandatory. Lastly, the need for written request to enroll, on a case by case basis, participants with location of the tumor not amenable to biopsy due to significant risk was removed.
5. Section 6.2 (Exclusion Criteria): Exclusion criterion 5.2 regarding Cohort A1 in the SAR444881 Dose Optimization (Sub-Part 2A) was modified to add RET mutations as an exclusion for participants with non-squamous NSCLC from this cohort.

6. Section 8.1 (Discontinuation from Study Treatment): Text was revised to state that the study treatment will be permanently discontinued in an appropriate manner in the case of pregnancy.
7. Section 9.4 (Management of Drug-Related Infusion Reactions): Section heading was updated to Management of Drug-Related Infusion Reactions and Cytokine Release Syndrome and guidance on grading and management strategy from the ASTCT Consensus Guidelines 2019 were added as Table 9.4-1.
8. Section 10.2.4 (Pregnancy): Section updated to align with change to Section 8.1.
9. Table 10.8-1 (Single Agent Dose Escalation [Sub-Part 1A] Biomarker Sampling Schedule): Removed dose optimization/expansion participants (Part 2) from footnote b as this table does not apply to these participants.
10. Table 10.8-4 (Dose Optimization/Expansion [Part 2] Biomarker Sampling Schedule): Footnotes c and d were updated to state that tumor tissue collection on treatment for these cohorts is per inclusion criteria (not mandatory).
11. Section 13 (REFERENCES): New reference was added.
12. Synopsis: Sections in the synopsis have been updated to align with protocol revisions.

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1 SYNOPSIS

Title of Study	A Phase 1/2, dose escalation, dose expansion, and dose optimization study of the safety, tolerability, and anti-tumor activity of SAR444881 administered alone and in combination with pembrolizumab, cetuximab, and/or chemotherapy in patients with advanced solid tumors
Protocol Number	TCD17465
NCT Number	NCT04717375
EU Trial Number	2023-504937-30
Investigational Product	SAR444881
Indication	Advanced solid tumors
Phase	1/2
Investigational Sites	Dose Escalation: The study will enroll participants in multiple sites in Israel and the US Dose Optimization/Expansion: The study will enroll participants in multiple sites in Europe, Asia, South America, and North America
Study Objectives	Dose Escalation (Sub-Parts 1A/1B/1C) Primary Objectives 1. To assess the safety and tolerability of SAR444881 when administered alone and in combination with pembrolizumab or with cetuximab 2. To determine the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAAD) and the recommended dose(s) of SAR444881 when administered alone and in combination with pembrolizumab or with cetuximab Secondary Objectives (all apply to SAR444881 monotherapy and SAR444881 in combination with pembrolizumab or with cetuximab) 1. To assess preliminary anti-tumor activity of SAR444881 2. To characterize the pharmacokinetics (PK) of SAR444881 3. To characterize the immunogenicity of SAR444881 Exploratory Objectives [REDACTED] [REDACTED] [REDACTED] [REDACTED] Dose Optimization/Expansion (Part 2) (all objectives apply to Dose Optimization [Sub-Part 2A; SAR444881 in combination with pembrolizumab, with cetuximab, or with pembrolizumab and chemotherapy] and Dose Expansion [Sub-Part 2B; SAR444881 monotherapy] unless otherwise specified) Primary Objectives 1. To assess preliminary anti-tumor activity of SAR444881

- To define the optimal dose of SAR444881 in combination with pembrolizumab, with cetuximab, or with pembrolizumab and chemotherapy (Sub-Part 2A only)

Secondary Objectives

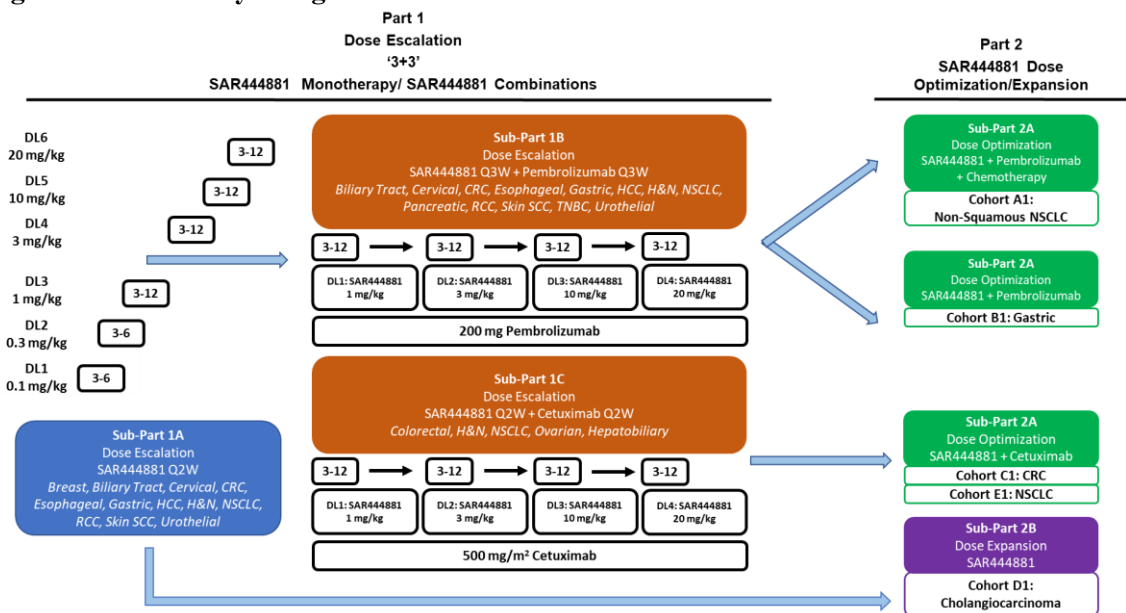
- To assess additional parameters of anti-tumor activity of SAR444881, including median progression free survival (PFS), PFS rate at defined intervals (3, 6, 9 and 12 months, and up to 24 months, per RECIST v1.1), and duration of response (DoR)
- To further assess the safety and tolerability of SAR444881
- To further characterize the PK of SAR444881
- To further characterize the immunogenicity of SAR444881

Exploratory Objectives

Methodology / Study Design

TCD17465 is an open-label, multicenter, Phase 1/2 first-in-human study of SAR444881, administered as a single agent and in combination with pembrolizumab, cetuximab, and/or chemotherapy, with a dose escalation phase (Part 1) and an optimization/expansion phase (Part 2). A study design schematic is presented in [Figure 1](#) and [Figure 5.2](#).

Figure 1: Study Design Schematic



DL, dose level; CRC, colorectal cancer; H&N, head and neck; HCC, hepato-cellular carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCC, squamous cell carcinoma

Dose Escalation Phase (Part 1): where the dose of SAR444881, administered alone and in combination with pembrolizumab or with cetuximab, is escalated to determine the Maximum Tolerated Dose (MTD) (or Maximum Administered Dose (MAAD), if no MTD is reached) and the recommended dose(s) of SAR444881 administered as a single agent and in combination.

In Sub-Part 1A, SAR444881 will be administered in escalating doses starting with 0.1 mg/kg, and continuing to 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg. Participants will be assigned to a

dose level in the order of study entry.

In Sub-Parts 1B and 1C, SAR444881 will be administered in escalating doses in combination with pembrolizumab and with cetuximab, respectively. Sub-Parts 1B and 1C will enroll in parallel and will start enrolling participants once a decision has been made to escalate SAR444881 to the 3 mg/kg dose level or once an MTD of lower than 3 mg/kg has been established in Sub-Part 1A. Sub-Parts 1B and 1C may start enrolling participants after a decision has been made to escalate SAR444881 to a higher dose level than 3 mg/kg dependent on Sub-Part 1A available safety data, e.g. occurrence of DLTs at 0.1 mg/kg, 0.3 mg/kg, or 1 mg/kg.

In Sub-Part 1B, the starting dose of SAR444881 will be 1 mg/kg or one dose level below the established SAR444881 monotherapy MTD, the lower of the two. The dose of SAR444881 will be escalated up to SAR444881 monotherapy MTD (or MAAD, if no MTD is reached) and all participants will be administered 200 mg of pembrolizumab Q3W. SAR444881 will be administered Q3W. A similar scheme will be used in Sub-Part 1C – the starting dose of SAR444881 will be 1 mg/kg or one dose level below the established SAR444881 monotherapy MTD, the lower of the two. The dose of SAR444881 will be escalated up to SAR444881 monotherapy MTD (or MAAD, if no MTD is reached). Cetuximab will be administered to all participants at a dose of 500 mg/m² Q2W. Premedication with a [REDACTED] will be given prior to each cetuximab dosing. SAR444881 will be administered Q2W.

Part 1 of this study uses a standard “3 + 3” dose escalation design with enrollment of at least 3 participants per dose level cohort.

“3 + 3” dose escalation will follow its conventional design: 3 participants will be enrolled in each dose level cohort unless a Dose-Limiting Toxicity (DLT) occurs, in which case the cohort will be expanded to 6 participants. If no additional DLT is observed in the expanded cohort, the next higher dose cohort will be opened for enrollment. Any cohort with ≥ 2 DLT out of 3 or 6 evaluable participants will have surpassed the MTD. The next lower dose cohort will be determined to be the MTD once it has been determined that no more than 1 of 6 participants has experienced a DLT. (note: if the next lower dose cohort only contains 3 participants, then 3 additional participants will be enrolled to have a total of 6 DLT evaluable participants at the MTD). The SAR444881 dose in combination cohorts will be escalated to a higher dose level only after the higher dose was evaluated in the corresponding Sub-Part 1A single agent dose escalation cohort and was determined to be safe by the Safety Review Committee (SRC).

During the dose escalation phase, a staggered dosing approach will be used. The first participants to be dosed at Cycle 1 Day 1 of each dose level will be observed for a minimum of 72 hours before additional participants (i.e. participant 2 onward in that cohort) receive study treatment at the same dose level. Escalation to the next cohort will only commence after a 4-week DLT observation period, beginning from the first study drug administration of the last participant of each cohort. If no DLTs are encountered in the 4-week DLT observation period, then the next cohort will be started, and the same pattern repeated.

Prior to dose escalation, the available safety data for all participants treated in the study to date, including the current dose cohort, will be evaluated by a SRC consisting of one or more independent oncology experts with substantial experience in the use of immunomodulatory oncology drugs, Principal Investigators, the study’s Medical Monitor, a Sponsor employee responsible for the clinical study or a Sponsor designee, and additional experts if required.

Intra patient SAR444881 dose escalation is allowed for Sub-Part 1A participants enrolled to the 0.1 mg/kg and 0.3 mg/kg dose level cohorts. Escalating the participant’s dose to the next dose level may occur only once the higher dose level has been defined as safe by the SRC and a decision has been made to further dose escalate. Intra patient dose escalation will be allowed up to 1 mg/kg. Intra patient dose de-escalation of SAR444881 is not allowed at any dose level.

Intermediate escalation dose levels may be added, based upon the clinical evaluation of all available safety and any available PK/pharmacodynamic data.

Once the tolerability (during the DLT evaluation) of a given SAR444881 dose of 1 mg/kg and above in either Sub-Part 1A, 1B, or 1C has been established, up to 6 additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles of SAR444881 administered

alone or in combination with pembrolizumab or with cetuximab.

The recommended dose(s) of SAR444881 as a single agent and in combination with pembrolizumab or with cetuximab will be determined at the end of each dose escalation sub-part through analysis of the totality of data including safety information, the MTD (or the MAAD, if no MTD is reached), efficacy data, PK, and pharmacodynamic data.

Dose-Limiting Toxicities: For the purpose of guiding decisions regarding dose escalation in Part 1, DLTs will be defined based on the incidence, intensity, and duration of AEs that are at least possibly related to the investigational treatment. The DLT period will start on the first day of Cycle 1 and end at Day 28 (therefore, 4 weeks). The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All drug-related AEs of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

A DLT will be defined as any drug-related AE during the 28 days starting with Day 1 of Cycle 1 (at any dose) that meets one or more of the criteria below:

- A treatment-emergent AE (TEAE) that in the opinion of a study investigator or the SRC is of clinical significance such that should be considered dose limiting;
- Hematological toxicity defined as:
 - Any Grade 4 neutropenia of 7 days or more in duration;
 - Any Grade 4 febrile neutropenia;
 - Any Grade 4 thrombocytopenia (platelets $\leq 25.0 \times 10^9/L$);
 - Any Grade 3 thrombocytopenia with bleeding;
 - Any Grade 4 anemia not explained by underlying disease.
- Any Grade 3 or higher non-hematological toxicity excluding the following:
 - Asymptomatic increases in liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, or gamma-glutamyl transferase) that resolve to baseline levels within 7 days;
 - Diarrhea or associated electrolyte abnormalities that can be controlled with adequate and optimal therapy when lasting < 72 hours; (note: persistent uncontrolled Grade 3 or higher diarrhea/electrolyte disturbances will be considered a DLT);
 - Nausea or vomiting that can be adequately controlled with optimal therapy and prophylaxis when lasting < 72 hours;
 - Grade 3 hyperglycemia in participants with diabetes mellitus or decreased glucose tolerance that is controlled pharmacologically;
 - Grade 3 or higher hypophosphatemia, hypomagnesemia, and hypocalcemia (without electrocardiogram [ECG] changes) that resolve with adequate treatment within 72 hours;
 - Grade 3 endocrinopathy that is well controlled by hormone replacement;
 - Grade 3 or Grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis;
 - Any other single laboratory value out of the normal range that has no clinical correlate and resolves with adequate medical management to Grade 1 or lower within 7 days;
 - Grade 3 rash that resolves to $\leq$ Grade 1 after a 1 to 2-week infusion delay of SAR444881 or SAR444881 and pembrolizumab. Topical steroid treatment is allowed for symptom control;
 - Cetuximab-related dermatologic toxicity not resulting in permanent discontinuation of cetuximab. Topical and systemic treatment for cetuximab-related dermatologic toxicity is allowed;

- Transient (≤ 24 hours) headache that resolves to Grade 1 or lower;
- Grade 3 fatigue when lasting < 7 days;
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor);
- Grade 3 fever not associated with hemodynamic compromise (e.g. hypotension, clinical or laboratory evidence of impaired end-organ perfusion);
- Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours.
- Any electrolyte abnormality associated with an electrocardiogram change requiring medical intervention
- Any death not clearly due to the underlying disease or extraneous causes.

In addition, for all cycles, the SRC may identify any event that is severe, life-threatening, or results in impairment of daily functions as a DLT, in which case, the next lower dose may be considered by the SRC as defining the MTD.

Dose Optimization/Expansion Phase (Part 2): to evaluate the preliminary anti-tumor activity of SAR444881 in specific tumor types and to gather additional safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) information and to define the optimal dose.

In Part 2, the proposed study aims to establish proof-of-concept using SAR444881 as either a monotherapy or in combination with one or more of the following: 1) the anti-PD1 monoclonal antibody pembrolizumab; 2) the anti-EGFR monoclonal antibody cetuximab; or 3) pembrolizumab and chemotherapy. Part 2 is divided into two sub-parts: in Sub-Part 2A (Dose Optimization), the preliminary anti-tumor activity and optimal dose of SAR444881 is assessed in combination with the aforementioned anti-tumor agents; and in Sub-Part 2B (Dose Expansion), the preliminary anti-tumor activity of SAR444881 is assessed as a monotherapy. The indications under investigation are described in [Table 1-1](#).

Table 1-1 - Overview of study cohorts

Cohort	Study Sub-Part	Study Intervention	Disease
A1	2A	SAR444881 + pembrolizumab + carboplatin + pemetrexed as 1L therapy	Non-squamous NSCLC
B1	2A	SAR444881 + pembrolizumab as 2L and later therapy	GC/GEJ
C1	2A	SAR444881 + cetuximab as a 2L and later therapy	CRC any <i>RAS</i>
D1	2B	SAR444881 as a 2L and later therapy	Cholangiocarcinoma
E1	2A	SAR444881 + cetuximab as 2L and later therapy	NSCLC

1L = first line; 2L = second line; NSCLC = non-small cell lung cancer; GC/GEJ = gastric cancer or gastro-esophageal junction adenocarcinoma; CRC = colorectal carcinoma.

In Sub-Part 2A, a two-stage design will be implemented to conduct dose optimization for each indication with combination therapy:

- **Stage 1 (Preliminary assessment):** Enroll 20 participants and treat the participants at one potential

- **Stage 2 (Randomization):** Randomize 40 participants 1:1 into the two recommended doses with each indication that showed activity in Stage 1 to support selection of optimal dose for the indication. In addition, it is possible that emerging data from Stage 1 may indicate the need to deviate from this randomization scenario. Based on the totality of data across the study as a whole and with agreement of the SRC, the Sponsor will retain flexibility on the design of the Stage 2, which may include, among other possibilities, a single dose level rather than randomization, or termination of the cohort prior to entry to Stage 2.

The study consists of a safety run-in and core phase for Cohort A1 (SAR444881 + pembrolizumab + carboplatin + pemetrexed for non-squamous NSCLC). Participants who fulfill the eligibility criteria of any cohort testing the regimen may be enrolled to the safety run-in of that regimen. The initial SAR444881 dose tested in the safety run-in for Cohort A1 will be 10 mg/kg. [REDACTED]

If 3 cases of deaths or treatment emergent life-threatening serious adverse events, considered at least possibly related to any drug in the trial treatment regimen, occur in a dose optimization or expansion cohort, further enrollment to the cohort will cease and enrollment to the other optimization/expansion cohorts will be interrupted. The findings will be shared with regulatory authorities and Institutional Review Boards/Independent Ethics Committees (IRB/IEC) and promptly discussed by the SRC. The SRC will review the available safety data for all participants treated to date in the study, consider whether study drug should be discontinued in all participants including those tolerating study treatment, consider if any protocol amendments are required to assure participant safety including revising inclusion or exclusion

	criteria, and discuss the risk-benefit balance of resuming enrollment. Enrollment will resume only upon recommendation by the SRC and after approval by regulatory authorities and IRB/IEC according to applicable local regulations. An overall design for dose optimization/expansion is presented in Figure 5.2. A schematic for study periods and participant flow is presented in Figure 5.3 for Cohorts C1, D1, and E1, and Figure 5.4 for Cohorts A1 and B1.
Key Inclusion and Exclusion Criteria	Inclusion Criteria: - Signed Written Informed Consent - Participants must have signed and dated an Institutional Review Board/Independent Ethics Committee approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care. - Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study - All single agent dose escalation (Sub-Part 1A) participants treated at SAR444881 dose levels equal and greater than 1 mg/kg (≥ 1 mg/kg) and all combination dose escalation (Sub-Parts 1B/1C) and dose optimization/expansion phase (Part 2) participants with low risk biopsies (i.e., expected rate of major complications $<0.5\%$, e.g., blood, bone marrow, skin, and superficial masses; Part 2 only) must consent and will be required to undergo mandatory pre- and on-treatment biopsies. In Part 2, participants with low risk biopsies who either do not consent to a pre-treatment tumor biopsy or do not have accessible qualifying lesions are not eligible. Moderate risk biopsies (i.e., expected rate of major complications 0.5-1.5%, e.g., intra-abdominal, some intrathoracic, and low risk procedures in patients with increased risk of bleeding or infection) are optional, and not mandatory (Part 2 only). High risk biopsies (i.e., expected rate of major complications $>1.5\%$) are not acceptable in this trial based on the current trial objectives (Part 2 only). - Type of Participant and Target Disease Characteristics - Patients with unresectable or metastatic disease who are refractory to or are not candidates for standard approved therapy (<u>all sub-parts and cohorts aside from Dose Optimization Cohort A1; Cohort A1 participants remain eligible to receive standard approved therapy</u>) - Participants with MSI-high (MSI-H) and/or MMR-deficient (dMMR) tumors or with tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] tumors should have received pembrolizumab or another anti-PD-1 or anti-PD-L1 therapeutic antibody, if are available as part of the local standard of care, prior to enrollment into this study - Participants must have histologic confirmation of malignancy - Participants must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Appendix 7) - All single agent dose escalation (Sub-Part 1A) participants treated at dose levels equal and greater than 1 mg/kg (≥ 1 mg/kg) and all combination dose escalation (Sub-Parts 1B/1C) and dose optimization/expansion phase (Part 2) participants must have at least one lesion accessible for biopsy

5. Eastern Cooperative Oncology Group Performance Status (ECOG) of 0 or 1 (see [Appendix 5](#))
6. Estimated life expectancy of more than 3 months
7. SAR444881 Monotherapy Dose Escalation (Sub-Part 1A) Tumor Types:
 - i. Breast cancer, cervical cancer, colorectal cancer, adenocarcinoma or squamous cell carcinoma of the esophagus, gastric or gastroesophageal junction adenocarcinoma, squamous cell carcinoma of the head and neck, hepatobiliary cancers (hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma), non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the skin, or urothelial carcinoma
8. SAR444881 in Combination with Pembrolizumab Dose Escalation (Sub-Part 1B) Tumor Types:
 - i. Cervical cancer, colorectal cancer, gastric or gastroesophageal junction adenocarcinoma, squamous cell carcinoma of the head and neck, hepatobiliary cancers (hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma), adenocarcinoma or squamous cell carcinoma of the esophagus, non-small cell lung cancer, pancreatic adenocarcinoma, renal cell carcinoma, squamous cell carcinoma of the skin, triple negative breast cancer, or urothelial carcinoma
9. SAR444881 in Combination with Cetuximab Dose Escalation (Sub-Part 1C) Tumor Types:
 - i. K-Ras wild-type colorectal cancer (right and left-sided tumors), squamous cell carcinoma of the head and neck, hepatobiliary cancers (hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma), non-small cell lung cancer, ovarian cancer
 1. Participants with BRAF-mutant colorectal cancer are eligible for enrollment
 - ii. Participants with prior exposure to EGFR inhibitors (including cetuximab) are allowed to enroll
10. SAR444881 Dose Optimization (Sub-Part 2A) Tumor Types:
 - i. Cohort A1:
 1. Histologically or cytologically confirmed diagnosis of Stage IV (per American Joint Committee on Cancer [AJCC] 8th edition [\[1\]](#)) non-squamous NSCLC,
 2. Prior anticancer therapy: 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.
 - ii. Cohort B1:
 1. Histologically or cytologically confirmed diagnosis of GC or Siewert Type 2 & 3 GEJ.
 2. Participants must have MSI status known, determined locally and must have non-MSI-H disease to be eligible.

3. Participants with unknown HER2/neu status must have their HER2/neu status determined locally. Participants previously treated with a trastuzumab-based regimen must have documentation of disease progression to be eligible.
4. Prior anticancer therapy: Participants should have received at least one prior line of treatment, including an anti-PD-1/PD-L1 containing regimen and have progressed after a primary or secondary resistance to an anti-PD-1/PD-L1.
 - i. Cohort C1:
 1. Histologically or cytologically confirmed diagnosis of colorectal cancer. Only participants with non-MSI-H disease are eligible.
 2. MSI status: Participants must have MSI status known or determined locally and must have non-MSI-H disease to be eligible.
 3. Participants with RAS-mutant and BRAF-mutant colorectal cancer are eligible for enrollment.
 4. Prior anticancer therapy: Participants should have failed or relapsed on at least 1 prior regimen.
 - a. Participants with RAS wild type colorectal cancer should have either failed or relapsed on or be ineligible for treatment with 5-fluorouracil, irinotecan, oxaliplatin, bevacizumab and anti-EGFR.
 - b. Participants with RAS-mutant colorectal cancer are eligible for enrollment; participants with RAS-mutant disease should have either failed or relapsed on or be ineligible for bevacizumab treatment.
 - c. Participants with BRAF-mutant colorectal cancer are eligible for enrollment; participants should have either failed or relapsed on treatment or be ineligible for treatment with encorafenib or other BRAF targeted therapies.
 - d. Once 10 participants that previously have not been exposed to cetuximab or other anti-EGFR therapy have been enrolled, enrollment will be limited to participants who have received cetuximab or other anti-EGFR therapy as part of their last line of treatment.
 - ii. Cohort E1:
 1. Histologically or cytologically confirmed NSCLC, Stage IV (per American Joint Committee on Cancer [AJCC] 8th edition [1]). Up to 10 participants with non-squamous NSCLC will be enrolled in Part 2, Stage 1, with the remaining enrollment allocated to participants with squamous NSCLC.
 2. Prior anticancer therapy: Participants should have failed or relapsed on at least 1 prior regimen.
 3. Participants with known driver alterations which include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Proto-oncogene tyrosine-protein kinase (ROS), BRAF, or RET mutation are

eligible for inclusion. Participants with driver mutations must have failed or relapsed on or are ineligible for available targeted therapies.

11. SAR444881 Dose Expansion Cohort D1 (Sub-Part 2B) Tumor Types:

- i. Histologically or cytologically confirmed advanced cholangiocarcinoma.
- ii. Participants must have received and progressed/been intolerant of at least 1 prior systemic therapy for metastatic and/or unresectable disease for whom all standard of care therapies have failed.

3. Physical and Laboratory Findings

1. Participants must have adequate organ function as defined by the following:

- i. Lymphocyte count $\geq 500/\text{mm}^3$
- ii. Neutrophil count $\geq 1,500/\text{mm}^3$
- iii. Platelet count $\geq 100,000/\text{mm}^3$
- iv. Hemoglobin concentration $\geq 9.0 \text{ g/dL}$
 - a. Criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin ($\geq$ approximately 3 months).
- v. $\text{AST/ALT} \leq 2.5 \times \text{ULN}$ or $\leq 5.0 \times \text{ULN}$ in participants with hepatocellular carcinoma, advanced cholangiocarcinoma or if liver metastases are present
- vi. Total bilirubin $\leq 1.5 \times \text{ULN}$ (except participants with Gilbert Syndrome who must have a total bilirubin level of $< 3.0 \times \text{ULN}$)
- vii. Creatinine clearance (observed or estimated using the Cockcroft–Gault equation) $\geq 45 \text{ mL/min}$ (Cohort A1 and D1 only)

4. Tumor Biopsies:

1. Dose Escalation:

- i. Participants in SAR444881 monotherapy dose escalation 0.1 mg/kg and 0.3 mg/kg dose level cohorts will be asked for their consent for optional pre- and on-treatment biopsies for performance of correlative tissue studies
- ii. All other participants must consent and will be required to undergo mandatory pre- and on-treatment biopsies for performance of correlative tissue studies
- iii. All participants will be asked for optional end of treatment biopsies

2. Dose Optimization/Expansion:

- i. **Mandatory baseline biopsy** for participants with low risk biopsies (i.e., expected rate of major complications $< 0.5\%$, e.g., blood, bone marrow, skin, and superficial masses) in **all dose optimization/expansion cohorts**: Tissue must be available for submission to the Sponsor. If sufficient sample is not available from biopsies collected in the last 6 months with no intervening therapy prior to consent, then the patient must be willing and able to undergo a biopsy for this collection.
- ii. Moderate risk biopsies (i.e., expected rate of major complications 0.5-1.5%, e.g., intra-abdominal, some intrathoracic, and low risk procedures

in patients with increased risk of bleeding or infection) are optional, and not mandatory. High risk biopsies (i.e., expected rate of major complications >1.5%) are not acceptable in this trial based on the current trial objectives.

- iii. **On-treatment biopsy** for at least 20 participants in **all dose optimization/expansion cohorts**, if clinically feasible, but may be optional before 20 biopsies have been obtained based on the totality of data at the sole discretion of the Sponsor
- iv. If imaging is required to obtain biopsy material, the biopsy should be performed using ultrasound guidance if feasible to prevent additional study-related radiation dose.

5. Age and Reproductive Status

- 1. Males and females, at least 18 years old
- 2. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment
- 3. Women must not be breastfeeding
- 4. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception ([Appendix 4](#)) for the duration of treatment with study treatment(s) and 10 months duration after last dose of study drug
- 5. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but still must undergo pregnancy testing
- 6. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception ([Appendix 4](#)) for the duration of treatment with study treatment and 7 months duration after the last dose of study drug. In addition, male participants must be willing to refrain from sperm donation during this time

Exclusion Criteria:

1. Medical Conditions

- 1. Active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
- 2. Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses < 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease
- 3. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (i.e., without evidence of progression) for at least 4 weeks by repeat imaging (Note: The repeat imaging should be performed during study screening.), clinically stable, and without requirement of steroid treatment for at least 14 days before the first dose of study intervention.
- 4. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

5. Non-hepatocellular carcinoma participants: acute or chronic hepatitis B virus (HBV) or hepatitis C virus infection (HCV)
6. Hepatocellular carcinoma participants: untreated active hepatitis B virus or dual infection with HBV/HCV or other hepatitis combinations or decompensated cirrhosis (Child Pugh B8 and higher)
7. Prior non-hematological malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
8. Prior hematological malignancy active within the previous 5 years
9. Participants after solid organ or allogeneic hematopoietic stem cell transplant
10. History of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting co-stimulation of immune cells or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g. hormone replacement after adrenal crisis)
11. History of Grade 3 or 4 infusion reaction, Grade 3 or 4 neurological toxicity, Grade 2, 3 or 4 myocarditis, Grade 4 nephritis, AST or ALT increases to more than 8 times ULN or total bilirubin increases to more than 3 times ULN, or Grade 4 colitis related to prior pembrolizumab or other anti-PD(L)-1 antibodies (for Sub-Part 1B, and Part 2 Cohorts A1 and B1)
12. History of life-threatening toxicity, Grade 3 or 4 infusion reaction, Grade 3 or 4 hypersensitivity reaction or three or more occurrences of Grade 3 or 4 dermatologic toxicity related to prior cetuximab or other anti-EGFR antibodies (for Sub-Part 1C, and Part 2 Cohorts C1 and E1)
13. History of clinically significant hypomagnesemia, hypocalcemia, or hypokalemia related to prior cetuximab or other anti-EGFR antibodies (for Sub-Part 1C, and Part 2 Cohorts C1 and E1)
14. History of Grade 2 or higher pneumonitis or interstitial lung disease
15. Unstable or deteriorating cardiovascular disease within the previous 6 months prior to screening including but not limited to the following:
 - i. Unstable angina or myocardial infarction;
 - ii. Transient ischemic attack (TIA)/cerebrovascular accident (CVA);
 - iii. Congestive heart failure (New York Heart Association [NYHA] Class III or IV);
 - iv. Uncontrolled clinically significant arrhythmias or arrhythmias requiring medication for rate control.
16. Any major surgery within 4 weeks of study drug administration. Participants must have recovered from the effects of major surgery at least 14 days before the first dose of the study drug
17. Any condition (including medical, emotional, psychiatric, or logistical) that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of study results

2. Prior/Concomitant Therapy

1. Immunosuppressive agents or immunosuppressive doses of systemic corticosteroids (except as permitted in the study protocol)

2. Cytotoxic anti-cancer agents, unless at least 4 weeks have elapsed from last dose of prior anti-cancer therapy and initiation of study therapy
3. Non-cytotoxic anti-cancer agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study therapy
4. Use of other investigational drugs (drugs not marketed for any indication) within 28 days before first study drug administration
5. Prior immune therapy treatments (for example, but not limited to: anti-CTLA-4, anti-PD-L1, anti-PD-L2, anti-PD-1, IL-2), unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of immune therapy and initiation of study therapy
6. Prior treatment with macrophage or NK cells activating therapies, e.g. drugs targeting CD-47, SIRP α , KIR, NKG2A
7. Inability to comply with restrictions and prohibited treatments as listed in [Section 7.10 Concomitant Therapy](#)
8. Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to study drug administration. Refer to [Section 7.10.1](#) for prohibited therapies.
9. Administration of a live attenuated vaccine within 28 days prior to the first dose of study therapy
10. Antibiotic use (excluding topical antibiotics) ≤ 14 days prior to first dose of IMP, or any serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV or oral antibiotics.
11. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis.

Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

3. Allergies and Adverse Drug Reactions

1. History of allergy or hypersensitivity to study drug components
2. Has severe hypersensitivity ($\geq$ Grade 3) to pembrolizumab and/or any of its excipients
3. History of any clinically significant drug allergy (such as anaphylaxis, hepatotoxicity, or hypersensitivity reactions) to other monoclonal antibodies

4. Pregnancy Exclusion

1. A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5. SAR444881 Dose Optimization (Sub-Part 2A):

1. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.

2. Cohort A1:

- i. Known driver alterations which include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Proto-oncogene tyrosine-protein kinase (ROS)1, BRAF, or RET mutation for participants with non-squamous NSCLC.
 - ii. 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).
 - iii. 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).
- 3. Cohorts A1 and E1:
 - i. Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of trial treatment.
- 4. Cohort C1:
 - i. Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD 1/PD-L1 but have written confirmation they were on control arm are allowed).
 - ii. The participant has clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months or high risk of uncontrolled arrhythmia or uncontrolled cardiac insufficiency.
 - iii. The participant has uncontrolled or poorly controlled hypertension (>180 mmHg systolic or > 130 mmHg diastolic).
 - iv. The participant has a history of allergic reactions attributed to compounds of chemical or biologic composition similar to those of cetuximab, or if the participant had red meat allergy/tick bite history.

Study Endpoints	Dose Escalation (Sub-Parts 1A/1B/1C) Primary Endpoints 1. Incidence of Serious Adverse Events (SAEs), incidence and severity of treatment-emergent AEs (TEAEs) coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the CTCAE v5.0, laboratory abnormalities classified by severity using CTCAE v5.0 2. Incidence of TEAEs meeting protocol defined DLT criteria Secondary Endpoints 1. Objective Response Rate (ORR) defined as the proportion of participants with a best overall response of Complete Response (CR) or Partial Response (PR) per RECIST v1.1 2. PK parameters of SAR444881 (C_{max}, C_{trough}, T_{max}, $T_{1/2}$, AUC) 3. Incidence of anti-drug antibodies (ADA) to SAR444881 Exploratory Endpoints [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Dose Optimization/Expansion (Part 2) Primary Endpoints 1. ORR per RECIST v1.1 (other datapoints may be utilized to supplement assessment of optimal SAR444881 dose) Secondary Endpoints 1. PFS defined as the time from the date of first dose of study drug to the date of first documented disease progression or death due to any cause, whichever occurs first, to estimate median PFS using Kaplan-Meier (K-M) methodology; PFS rate at 3, 6, 9, 12 months, and up to 24 months per RECIST v1.1; Disease Control Rate (DCR, rate of CR, PR or Stable Disease (SD)); Duration of Response (DoR) defined as the duration between first documentation of CR or PR to first documentation of disease progression or death from any cause, whichever occurs first 2. Incidence of SAEs and TEAEs, as described above 3. PK parameters of SAR444881 (C_{max}, C_{trough}, T_{max}, $T_{1/2}$, AUC) 4. Incidence of ADA to SAR444881 Exploratory Endpoints [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
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Duration of Treatment	Participants in the study will complete up to 3 periods in the study: 1. Screening: The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). 2. Treatment: All participants will be treated until meeting criteria for discontinuation. Discontinuation criteria include disease progression, intolerance to therapy, start of a new anti-cancer therapy, withdrawal of consent, or Investigator or Medical Monitor determines that continued participation in the study is not in the best interest of the participant. Participants will be permitted to continue treatment beyond RECIST v1.1 defined Progressive Disease (PD) if they meet specific criteria defined in the study protocol. The dosing regimen of SAR444881 is Q2W in all study cohorts except Sub-Part 1B (pembrolizumab combination escalation) and Sub-Part 2A Dose Optimization cohorts A1 and B1 in which SAR444881 will be administered Q3W. In combination cohorts, participants will be treated with pembrolizumab Q3W and/or cetuximab Q2W (Dose Escalation Sub-Part 1C, Dose Optimization Cohort C1 and E1, and Dose Expansion Cohort D1). Each cycle of the treatment period will be 4 weeks in length in all study cohorts except Sub-Part 1B and Sub-Part 2A Dose Optimization cohorts A1 and B1 in which a treatment cycle will be 3 weeks. The maximum duration of treatment will not exceed 2 years or 35 cycles for participants enrolled onto Cohorts A1 and B1. 3. Safety Follow-up: - Once the decision is made to discontinue the participant from treatment, all participants will enter a safety follow up period. - An EOT visit will be completed for all participants and this visit will be considered the start of the safety follow up period. - After the EOT visit, all participants will be evaluated for any new AEs for at least 90 days after the last dose of study treatment. Follow up visits should occur at Days 30, 60 and 90 (± 7 days for each visit) after the EOT visit. All participants will be required to complete the 3 clinical safety follow up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation. Participants with an ongoing AE, at least possibly related to study drug, should continue to be followed until resolution, stabilization or the AE is deemed irreversible.
Study Duration	Estimated Study Duration: Dose Escalation (Part 1): Approximately 34 months Dose Optimization/Expansion (Part 2): Approximately 28 months

Number of Participants	SAR444881 Dose Escalation (Part 1): The sample size for Part 1 of this study was determined by clinical rather than statistical considerations. The estimated number of participants in each sub-part is based on a standard “3 + 3” design enrolling up to 6 participants per dose level cohort. Additional participants may be enrolled in SAR444881 monotherapy (Sub-Part 1A) dose levels of 1 mg/kg and above and in all SAR444881 combinations dose levels (Sub-Parts 1B/1C) to better characterize the safety, PK, and pharmacodynamic profiles of SAR444881 (a maximum of 6 additional participants in each dose level cohort). Up to 156 participants will be enrolled in Part 1 – up to 60 participants will be treated across six planned dose levels in Sub-Part 1A and up to 48 participants in Sub-Parts 1B and 1C each across four planned dose levels. SAR444881 Dose Optimization/Expansion (Part 2): In Sub-Part 2A (Dose Optimization), 20 participants will be enrolled at one dose level for each indication at Stage 1. For those indications showed activity in Stage 1, 40 participants with 1:1 randomization into two dose levels will be included in the Stage 2. The sample size for each indication will be ranged from 20 to 60 participants. In Sub-Part 2B, 20 participants will be enrolled at one dose level to receive SAR444881 monotherapy. If activity is observed in these first 20 participants, a further 20 to 40 participants will be enrolled. With a sample size of 40 study participants, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively. Interim analyses will be conducted at the end of stage 1 for each cohort. Bayesian toxicity monitoring on DLT is used to determine the stopping boundaries for safety issues.																											
Study Treatment and Mode of Administration	<table><tr><th>Study Drug</th><th>Dosage Level(s)</th><th>Frequency of Administration</th><th>Route of Administration</th></tr><tr><td>SAR444881</td><td><u>Escalation:</u> Sub-Part 1A: 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg Sub-Parts 1B/1C: 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg <u>Optimization/Expansion (Part 2, Stage 1):</u> 10 mg/kg (all cohorts)</td><td>Sub-Parts 1A/1C and Part 2 Cohorts C1, D1, and E1: Q2W Sub-Part 1B and Part 2 Cohorts A1 and B1: Q3W</td><td>IV</td></tr><tr><td>Pembrolizumab</td><td>200 mg</td><td>Q3W</td><td>IV</td></tr><tr><td>Cetuximab</td><td>Escalation and Optimization Cohort C1: 500 mg/m²</td><td>Q2W</td><td>IV</td></tr><tr><td>Carboplatin</td><td>AUC of 5</td><td>Q3W for 4 cycles</td><td>IV</td></tr><tr><td>Pemetrexed</td><td>500 mg/m²</td><td>Q3W</td><td>IV</td></tr></table>	Study Drug	Dosage Level(s)	Frequency of Administration	Route of Administration	SAR444881	<u>Escalation:</u> Sub-Part 1A: 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg Sub-Parts 1B/1C: 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg <u>Optimization/Expansion (Part 2, Stage 1):</u> 10 mg/kg (all cohorts)	Sub-Parts 1A/1C and Part 2 Cohorts C1, D1, and E1: Q2W Sub-Part 1B and Part 2 Cohorts A1 and B1: Q3W	IV	Pembrolizumab	200 mg	Q3W	IV	Cetuximab	Escalation and Optimization Cohort C1: 500 mg/m ²	Q2W	IV	Carboplatin	AUC of 5	Q3W for 4 cycles	IV	Pemetrexed	500 mg/m ²	Q3W	IV	SAR444881 will be infused over ■ minutes at all dosage levels except for the 0.1 mg/kg dosage which will be infused over ■ minutes. Pembrolizumab, cetuximab, carboplatin, and pemetrexed will be administered according to their recommended dosage and administration including use of premedication. No dose reduction for pembrolizumab is allowed. Cetuximab dosage may be modified for adverse reactions management in accordance with the drug’s Prescribing Information.		
Study Drug	Dosage Level(s)	Frequency of Administration	Route of Administration																									
SAR444881	<u>Escalation:</u> Sub-Part 1A: 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg Sub-Parts 1B/1C: 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg <u>Optimization/Expansion (Part 2, Stage 1):</u> 10 mg/kg (all cohorts)	Sub-Parts 1A/1C and Part 2 Cohorts C1, D1, and E1: Q2W Sub-Part 1B and Part 2 Cohorts A1 and B1: Q3W	IV																									
Pembrolizumab	200 mg	Q3W	IV																									
Cetuximab	Escalation and Optimization Cohort C1: 500 mg/m ²	Q2W	IV																									
Carboplatin	AUC of 5	Q3W for 4 cycles	IV																									
Pemetrexed	500 mg/m ²	Q3W	IV																									

	In combination cohorts drug administration visits, pembrolizumab or cetuximab will be infused [REDACTED] SAR444881. The SAR444881 infusion will start at least [REDACTED] All participants administered cetuximab will be premedicated with a [REDACTED] intravenously (e.g., diphenhydramine 50 mg) 30–60 minutes prior to each cetuximab dosing. Premedication for participants in cohort A1 receiving pemetrexed include folic acid, vitamin B12, and dexamethasone. Further details of pemetrexed premedication are described in Section 7.4.4.1. For all study participants, SAR444881 infusions will require a [REDACTED] following the completion of the infusion for the first [REDACTED] for all subsequent doses. Cohort A1 dosing sequence: [REDACTED]
Discontinuation from Treatment	All participants will be treated until meeting criteria for discontinuation. Discontinuation criteria include: • Disease progression • Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator or the Medical Monitor, indicates that continued participation in the study is not in the best interest of the participant • Withdrawal of consent • New anti-cancer therapy is initiated • Clinical deterioration while receiving active study therapy • Drug related AE occurring at any time that meets DLT criteria • Inability to comply with protocol • Termination of the study by Sponsor • Completion of 35 cycles for participants in Cohort A1 and B1 or 2 years of treatment for Cohorts C1, D1, and E1. Participants in SAR444881 combination cohorts meeting any of the discontinuation criteria will be required to permanently discontinue all assigned study drugs. However, if discontinuation is due to toxicity and the toxicity is considered related to one study drug while clinical benefit has been observed, treatment with the study drug to which the toxicity is attributed must be discontinued but may be continued for the other study drug after discussion and agreement with the Medical Monitor. Participants will be permitted to continue treatment beyond initial RECIST v1.1 defined Progressive Disease (PD) if they meet specific criteria defined in the study protocol.
Safety Assessment	Safety assessments will be based on reported AEs and the measurement results of vital signs, electrocardiograms, physical examinations, and clinical laboratory tests. Safety assessments will also include evaluations of the immune safety profile of SAR444881 as noted by immune mediated AEs and laboratory tests for immunogenicity and immunotoxicity. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for [REDACTED] days after the last dose of SAR444881 in monotherapy cohorts and after the last dose of SAR444881, pembrolizumab, cetuximab, carboplatin, or pemetrexed in combination therapy cohorts. All adverse events, regardless of relationship to study drug(s), should be collected throughout the safety follow-up period. Local laboratories will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using NCI CTCAE v5.0. Safety parameters will be summarized using descriptive statistics. Parameters include adverse events,

	clinical laboratory tests, physical examinations, vital signs, ECOG performance status, ECGs, immune safety, cytokines and immunogenicity tests. A Safety Review Committee (SRC) consisting of one or more independent oncology experts with substantial experience in the use of immunomodulatory oncology drugs, Principal Investigators, the study's Medical Monitor, a Sponsor employee responsible for the clinical study (or a Sponsor designee), and additional experts if required will be set up and convene at regular intervals. The SRC will act in an advisory capacity to the Sponsor and will monitor participant safety and evaluate the available preliminary efficacy data for the study. The SRC will provide oversight of safety and preliminary efficacy considerations and provide advice to the Sponsor regarding actions the SRC deems necessary for the continued protection of participants enrolled in the study.
Pharmacokinetics Assessment	The PK of SAR444881 will be derived from serum concentration vs. time data. The PK parameters that will be assessed may include, but are not limited to, maximum observed serum concentration (C_{max}), concentration observed at the end of an intravenous (IV) infusion (C_{eoi}), serum concentration at the end of the dosing interval (C_{trough}), time of maximum observed serum concentration (T_{max}), area under the serum concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration, and terminal elimination half-life. All-peak and trough pharmacokinetic serum concentration values will be summarized using descriptive statistics.
Immunogenicity Assessment	Serum samples for SAR444881 anti-drug antibodies (ADA) will be collected from all participants at specified timepoints.
Efficacy Assessment	Efficacy assessments of the anti-tumor activity of SAR444881 monotherapy and SAR444881 combinations will be based on tumor measurements, using RECIST v1.1, with computed tomography and/or magnetic resonance imaging, as appropriate. Assessments will be completed at baseline and Q8W (± 1 week) for the first 24 weeks and then Q12W (± 2 weeks) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. Major statistical analyses will be descriptive. The efficacy parameter ORR (rate of participants achieving Complete Response (CR) or Partial Response (PR)) will be summarized using descriptive statistics with estimation of exact 95% confidence interval. Duration of Response (DoR), defined as the duration between first documentation of CR or PR to first documentation of disease progression or death from any cause, whichever occurs first, will be summarized with descriptive statistics using Kaplan-Meier methods. Disease Control Rate (DCR, rate of CR, PR or Stable Disease (SD)) will also be similarly summarized. Best Overall Response (BOR, either CR, PR, SD or Progressive Disease (PD)) will be described for each participant. Time to response and duration of response will be summarized for those participants with confirmed responses. Progression Free Survival (PFS) will be estimated using the Kaplan-Meier methodology.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline: Part 1 (Escalation) and Part 2 (Optimization/Expansion)²

Procedure	Screening Visit (Days -28 to -1)	Notes
Eligibility Assessments		
Informed Consent/enrollment/randomization	X	A participant is considered enrolled only when participant has completed all the necessary screening procedure, is deemed eligible and a protocol-specific informed consent is signed. Part 1 of the study is not randomized and no IRT system will be used. Part 2: Some cohort(s) may be randomized. All eligible participants must be randomized/enrolled using Interactive Response Technology.
Inclusion/Exclusion Criteria	X	See Section 6.1 and 6.1 .
Demographics/Medical History	X	See Section 5.1.1.1 .
Prior Cancer Therapies	X	
ECOG Performance Status	X	See Appendix 5 .
Safety Assessments		
Physical Examination	X	If the screening PE is performed within 72 hours prior to dosing on Day 1 then a single examination may count as both the screening and pre-dose evaluation.
Physical Measurements	X	Includes height and weight. If performed within 72 hours prior to dosing on Day 1 then a single measurement may count as the screening and pre-dose evaluation.
Vital Signs	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Concomitant Medication Use	X	Concomitant medications should be recorded at baseline and throughout the study. Medications taken within 4 weeks prior to study drug administration must be recorded as well. See Section 7.10 .
Electrocardiogram	X	12-lead ECG at Screening. ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 10.5.1 .
LVEF ¹	X	See Section 10.5.1

Table 2-1: Screening Procedural Outline: Part 1 (Escalation) and Part 2 (Optimization/Expansion)²

Procedure	Screening Visit (Days -28 to -1)	Notes
Hematology/Chemistry/Liver Function Tests (LFTs)/Serology/Urinalysis	X	Includes blood and urine samples. See Clinical Laboratory Assessments in Section 10.5.6 .
Coagulation Profile	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Thyroid Function Tests	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Pregnancy Test	X	For WOCBP only. Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If pregnancy test is taken within 72 hours of dosing (C1D1), a further pregnancy test is not required.
Follicle Stimulating Hormone	X	Women only as needed to document postmenopausal status. Refer to Appendix 4 .
Adverse Event Reporting		
Assessment of Signs, Symptoms, and Clinical Complaints	X	
Monitor for Serious Adverse Events	X	After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (e.g. SAE related to invasive procedures such as biopsies). Any other adverse event should not be reported.
Tumor Assessments		
Body Imaging	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, should be performed within 28 days prior to date of first dose. <u>For head and neck cancer participants</u> : CT/MRI of the neck should also be performed within 28 days prior to the date of first dose. See Section 10.1.1 for further details.
Bone Scan	X	As clinically indicated per local standards. See Section 10.1.1 .

Table 2-1: Screening Procedural Outline: Part 1 (Escalation) and Part 2 (Optimization/Expansion)²

Procedure	Screening Visit (Days -28 to -1)	Notes
Biomarker Assessments		
Tumor Biopsy		
Documentation of Microsatellite instability (MSI) and/or DNA mismatch repair (MMR) tumor status		
Documentation of KRAS mutation tumor status		

Abbreviations: C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; hCG = human chorionic gonadotropin; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PE = physical examination; SAE = serious adverse event; WOCBP = women of child bearing potential

²Minimum screening duration for Part 2 is 11 days. A maximum of 11 days is required to get IMP on site. Randomization of the participant must take this constraint into consideration

Table 2-2: On-Treatment Outline – Sub-Parts 1A/1C: SAR444881 Monotherapy and SAR444881 in Combination with Cetuximab Dose Escalation

Procedure	Cycle 1 (28 Days)					Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^b)	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Safety Assessments													
Physical Examination	X	X	X	X		X		X		X		X	If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or serious adverse event CRF page.
Target Physical Exam					X		X		X		X		Targeted to signs and symptoms
Physical Measurements	X		X	X	X	X	X	X	X	X	X	X	Weight only
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. See Section 10.5.3 for vital signs measurement schedule at study drug administration visits.
ECOG	X					X				X		X	See Appendix 5 for details
Electrocardiogram	X		X	X		X		X		X	X	X	12-lead ECG. Pre- and post-infusion on Cycle 1 Day 1 and Cycle 1 Day 15. Pre-infusion at all other study drug administrations. ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 10.5.1 , Table 10.5-1 and Table 10.5-3 .
Hematology/Chemistry/LFTs	X	X	X	X	X	X	X	X	X	X	X	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Coagulation Profile	X			X		X				X		X	See Clinical Laboratory Assessments in Section 10.5.6 .
Urinalysis	X			X		X		X		X		X	See Clinical Laboratory Assessments in Section 10.5.6 .

Table 2-2: On-Treatment Outline – Sub-Parts 1A/1C: SAR444881 Monotherapy and SAR444881 in Combination with Cetuximab Dose Escalation

Procedure	Cycle 1 (28 Days)					Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^b)	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Thyroid Function Tests	X									X		X	If collected at screening, do not repeat on Cycle 1 Day 1. Collect every 2 cycles, pre-dose, beginning with Cycle 3 Day 1 and at EOT. To include TSH with reflex testing (free T3 and free T4) if TSH is abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test	X					X				X		X	For WOCBP only. Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). Pregnancy test must be done within 72 hours prior to study drug administration.
Adverse Event Reporting													
Monitor for Serious and Non-Serious Adverse Events	X											See Section 10.2 . AEs should be followed until resolved to baseline, stabilized, or deemed irreversible.	
Sample Collection													
Pharmacokinetic and Immunogenicity/ADA Sampling	See notes											See Section 10.6 , Section 10.7 , Table 10.5-1 and Table 10.5-3 .	

Table 2-2: On-Treatment Outline – Sub-Parts 1A/1C: SAR444881 Monotherapy and SAR444881 in Combination with Cetuximab Dose Escalation

Procedure	Cycle 1 (28 Days)					Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^b)	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Biomarker Assessments: Blood and Serum Pharmacodynamic Sampling													
Efficacy Assessments													
Body Imaging	See notes											Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. <u>For head and neck cancer participants:</u> In addition, CT/MRI of the neck should also occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, death, or initiation of another systemic anti-cancer treatment. Additional imaging may be performed as clinically indicated. See Section 10.1.1 for further details.	

Table 2-2: On-Treatment Outline – Sub-Parts 1A/1C: SAR444881 Monotherapy and SAR444881 in Combination with Cetuximab Dose Escalation

Procedure	Cycle 1 (28 Days)					Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^b)	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Bone Scan	See notes											As clinically indicated per local standards. See Section 10.1.1 .	
Tumor Biopsy								X				X	On-treatment tumor biopsy is optional in Sub-Part 1A 0.1 mg/kg and 0.3 mg/kg dose level cohorts. On-treatment tumor biopsy is mandatory in Sub-Part 1A SAR444881 dose level cohorts of 1 mg/kg and above and for all Sub-Part 1C participants. End of treatment biopsy is optional for all dose level cohorts. See Section 10.8 for details of biopsy collection and specimen handling. Complete instructions on tissue collection, processing, handling, and shipment of all biopsy samples are provided in the Laboratory Manual.
Concomitant Medication Use	X											See Section 7.10 .	
Clinical Drug Supplies													
SAR444881 Administration	SAR444881 will be administered Q2W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .												Sub-Parts 1A/1C
Cetuximab Administration	Cetuximab will be administered Q2W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .												Sub-Part 1C

Abbreviations: ADA = anti-drug antibody; AE = adverse event; C = cycle; CRF = case report form; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment (last administration of study drug); hCG = human chorionic gonadotropin; LFTs = liver function tests; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q2W = every two weeks; TSH = thyroid stimulating hormone; WOCBP = women of child bearing potential.

^a Refer to [Table 2-6](#) and [Section 5](#) for Follow-Up Period

^b Changes to the timing of Cycle 1 visits require approval by the Sponsor

Table 2-3: On Treatment Outline – Sub-Part 1B: SAR444881 in Combination with Pembrolizumab Dose Escalation

Procedure	Cycle 1 (21 Days)				Cycle 2 (21 Days)			Cycle 3 (21 Days)		Cycle 4 and beyond (21 Days)	EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^c)	D 1	D 2	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 1		
Safety Assessments												
Physical Examination	X	X	X	X	X	X		X		X	X	If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or serious adverse event CRF page.
Target Physical Exam							X		X			Targeted to signs and symptoms
Physical Measurements	X		X	X	X	X	X	X	X	X	X	Weight only
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. See Section 10.5.3 for vital signs measurement schedule at study drug administration visits.
ECOG	X				X			X		X	X	See Appendix 5 for details
Electrocardiogram	X		X	X	X	X		X	X	X	X	12-lead ECG. Pre- and post-infusion on Cycle 1 Day 1 and Cycle 2 Day 1. Pre-infusion at all other study drug administrations. ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 10.5.1 and Table 10.5-2 .
Hematology/Chemistry/LFTs	X	X	X	X	X	X	X	X	X	X	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Coagulation Profile	X			X		X		X		X	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Urinalysis	X			X	X		X	X		X	X	See Clinical Laboratory Assessments in Section 10.5.6 .

Table 2-3: On-Treatment Outline – Sub-Part 1B: SAR444881 in Combination with Pembrolizumab Dose Escalation

Procedure	Cycle 1 (21 Days)				Cycle 2 (21 Days)			Cycle 3 (21 Days)		Cycle 4 and beyond (21 Days)	EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^c)	D 1	D 2	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 1		
Thyroid Function Tests	X				X			X		X	X	If collected at screening, do not repeat on Cycle 1 Day 1. Collect every cycle, pre-dose and at EOT. To include TSH with reflex testing (free T3 and free T4) if TSH is abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test	X				X			X		X	X	For WOCBP only. Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). Pregnancy test must be done within 72 hours prior to study drug administration.
Adverse Event Reporting												
Monitor for Serious and Non-Serious Adverse Events	X											See Section 10.2 . AEs should be followed until resolved to baseline, stabilized, or deemed irreversible.
Sample Collection												
Pharmacokinetic and Immunogenicity/ADA Sampling	See notes											See Section 10.6 , Section 10.7 and Table 10.5-2 .

Table 2-3: On Treatment Outline – Sub-Part 1B: SAR444881 in Combination with Pembrolizumab Dose Escalation

Procedure	Cycle 1 (21 Days)				Cycle 2 (21 Days)			Cycle 3 (21 Days)		Cycle 4 and beyond (21 Days)	EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^c)	D 1	D 2	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 1		
Biomarker Assessments: Blood and Serum Pharmacodynamic Sampling												
Efficacy Assessments												
Body Imaging	See notes											Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. <u>For head and neck cancer participants:</u> In addition, CT/MRI of the neck should also occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, death, or initiation of another systemic anti-cancer treatment. Additional imaging may be performed as clinically indicated. See Section 10.1.1 for further details.

Table 2-3: On-Treatment Outline – Sub-Part 1B: SAR444881 in Combination with Pembrolizumab Dose Escalation

Procedure	Cycle 1 (21 Days)				Cycle 2 (21 Days)			Cycle 3 (21 Days)		Cycle 4 and beyond (21 Days)	EOT ^a	Notes
+/- 2 days (for visits except Cycle 1 ^c)	D 1	D 2	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 1		
Bone Scan	See notes										As clinically indicated per local standards. See Section 10.1.1 .	
Tumor Biopsy									X ^b		X	On-treatment tumor biopsy is mandatory for all Sub-Part 1B participants. End of treatment biopsy is optional for all SAR444881 dose level cohorts. See Section 10.8 for details of biopsy collection and specimen handling. Complete instructions on tissue collection, processing, handling, and shipment of all biopsy samples are provided in the Laboratory Manual.
Concomitant Medication Use	X										See Section 7.10 .	
Clinical Drug Supplies												
SAR444881 Administration	SAR444881 will be administered Q3W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .											
Pembrolizumab Administration	Pembrolizumab will be administered Q3W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .											

Abbreviations: ADA = anti-drug antibody; AE = adverse event; C = cycle; CRF = case report form; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; hCG = human chorionic gonadotropin; LFTs = liver function tests; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3W = every three weeks; TSH = thyroid stimulating hormone; WOCBP = women of child bearing potential.

^a Refer to [Table 2-6](#) and [Section 5](#) for Follow-Up Period

■
^c Changes to the timing of Cycle 1 visits require approval by the Sponsor

Table 2-4: On Treatment Procedural Outline – Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1, and E1

Procedure	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Safety Assessments												
Physical Examination	X				X				X		X	See Screening notes
Target Physical Exam		X	X	X		X	X	X		X		Targeted to signs and symptoms
Physical Measurements	X		X		X		X		X	X	X	Weight only
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. See Section 10.5.3 for vital signs measurement schedule at study drug administration visits.
ECOG	X				X				X		X	See Appendix 5 for details
Electrocardiogram	X				X						X	Pre-infusion 12-lead ECG. ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 10.5.1 and Table 10.5-4 .
Hematology/Chemistry/ LFTs	X	X	X	X	X	X	X	X	X	X	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Coagulation Profile	X				X				X		X	See Clinical Laboratory Assessments in Section 10.5.6 .
Urinalysis	X				X				X		X	See Clinical Laboratory Assessments in Section 10.5.6 .
Thyroid Function Tests	X								X		X	TSH with reflex testing (free T3 and free T4) if TSH is abnormal. Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT.

Table 2-4: On-Treatment Procedural Outline - Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1, and E1

Procedure	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes	
	+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1			D 15
Pregnancy Test	X				X					X		X	For WOCBP only. Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). Pregnancy test must be done within 72 hours prior to study drug administration.
Adverse Event Reporting													
Monitor for Serious and Non-Serious Adverse Events	X												See Section 10.2 . AEs should be followed until resolved to baseline, stabilized, or deemed irreversible.
Sample Collection													
Pharmacokinetic and Immunogenicity/ADA Sampling	See notes												See Section 10.6 , Section 10.7 and Table 10.5-4 .

Table 2-4: On Treatment Procedural Outline - Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1 and E1

Procedure	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Biomarker Assessments: Blood and Serum Pharmacodynamic Sampling												
Efficacy Assessments												
Body Imaging	See notes										Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. <u>For head and neck cancer participants:</u> In addition, CT/MRI of the neck should also occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. See Section 10.1.1 for further details.	

Table 2-4: On-Treatment Procedural Outline - Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1, and E1

Procedure	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
Bone Scan	See notes										As clinically indicated per local standards. See Section 10.1.1 .	
Tumor Biopsy							X ^c				See Section 10.8 for details of biopsy collection and specimen handling. Complete instructions on tissue collection, processing, handling, and shipment of all biopsy samples are provided in the Laboratory Manual.	
Concomitant Medication Use	X										See Section 7.10 .	
[REDACTED]												
[REDACTED]	[REDACTED]											
Clinical Drug Supplies												
SAR444881 Administration	SAR444881 will be administered Q2W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .											

Table 2-4: On-Treatment Procedural Outline - Sub-Part 2A/B: SAR444881 Dose Optimization/Expansion Cohorts C1, D1, and E1

Procedure	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Cycle 3 and beyond (28 Days)		EOT ^a	Notes
	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15		
SAR444881 Administration	SAR444881 will be administered Q2W beginning on Cycle 1 Day 1. Refer to Section 5.1.2.											
Cetuximab Administration	Cetuximab will be administered Q2W beginning on Cycle 1 Day 1. Refer to Section 5.1.2.											Cohorts C1 and E1 only

^a Refer to [Table 2-6](#) and [Section 5](#) for Follow-Up period

^c [REDACTED] On-treatment biopsy for at least 20 total participants in all dose optimization/expansion cohorts, if clinically feasible. All participants with low risk biopsies (i.e., expected rate of major complications <0.5%, e.g., blood, bone marrow, skin, and superficial masses) must consent and will be required to undergo mandatory pre- and on-treatment biopsies. Moderate risk biopsies (i.e., expected rate of major complications 0.5-1.5%, e.g., intra-abdominal, some intrathoracic, and low risk procedures in patients with increased risk of bleeding or infection) are optional, and not mandatory. High risk biopsies (i.e., expected rate of major complications >1.5%) are not acceptable in this trial based on the current trial objectives.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; C = cycle; CT = computed tomography; D = Day; EOI = end of infusion; EOT = end of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; [REDACTED]; [REDACTED] (version 2); Q2W = every two weeks; TSH = thyroid stimulating hormone; WOCBP = women of child bearing potential

Table 2-5: On-Treatment Procedural Outline – Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1

Procedure	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Cycle 3 and beyond (21 Days)		EOT ^a	Notes
+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8		
Safety Assessments										
Physical Examination	X			X			X		X	See Screening notes
Target Physical Exam		X	X		X	X		X		Targeted to signs and symptoms
Physical Measurements	X		X	X		X	X	X	X	Weight only
Vital Signs	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. See Section 10.5.3 for vital signs measurement schedule at study drug administration visits.
ECOG	X			X			X		X	See Appendix 5 for details
Electrocardiogram	X			X					X	Pre-infusion 12-lead ECG. ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 10.5.1 and Table 10.5-5 . ECGs may be performed as clinically necessary at other timepoints.
Hematology/Chemistry/LFTs	X	X	X	X	X	X	X	X	X	See Clinical Laboratory Assessments in Section 10.5.6 .
Coagulation Profile	X			X			X		X	See Clinical Laboratory Assessments in Section 10.5.6 .
Urinalysis	X			X			X		X	See Clinical Laboratory Assessments in Section 10.5.6 .
T3, FT4, TSH, and cortisol	X						X		X	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.

Table 2-5: On-Treatment Procedural Outline - Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1

Procedure	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Cycle 3 and beyond (21 Days)		EOT ^a	Notes
+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8		
Pregnancy Test	X			X			X		X	For WOCBP only. Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). Pregnancy test must be done within 72 hours prior to study drug administration.
Adverse Event Reporting										
Monitor for Serious and Non-Serious Adverse Events	X									See Section 10.2 . AEs should be followed until resolved to baseline, stabilized, or deemed irreversible.
Sample Collection										
Pharmacokinetic and Immunogenicity/ADA Sampling	See notes									See Section 10.6 , Section 10.7 and Table 10.5-5 .

Table 2-5: On-Treatment Procedural Outline - Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1

Procedure	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Cycle 3 and beyond (21 Days)		EOT ^a	Notes
+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8		
Biomarker Assessments: Blood and Serum Pharmacodynamic Sampling										
Efficacy Assessments										
Body Imaging	See notes									Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. <u>For head and neck cancer participants:</u> In addition, CT/MRI of the neck should also occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. See Section 10.1.1 for further details.

Table 2-5: On-Treatment Procedural Outline - Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1

Procedure	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Cycle 3 and beyond (21 Days)		EOT ^a	Notes
	+/- 2 days (for all visits except C1D1)	D 1	D 8	D 15	D 1	D 8	D 15	D 1		
Bone Scan	See notes									As clinically indicated per local standards. See Section 10.1.1 .
Tumor Biopsy								X ^c		See Section 10.8 for details of biopsy collection and specimen handling. Complete instructions on tissue collection, processing, handling, and shipment of all biopsy samples are provided in the Laboratory Manual.
Concomitant Medication Use	X									See Section 7.10 .
[REDACTED]										
[REDACTED]	[REDACTED]									
Clinical Drug Supplies										
SAR444881 Administration	SAR444881 will be administered Q3W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .									

Table 2-5: On-Treatment Procedural Outline - Sub-Part 2A: SAR444881 Dose Optimization Cohorts A1 and B1

Procedure	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Cycle 3 and beyond (21 Days)		EOT ^a	Notes
	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8		
Pembrolizumab Administration	Pembrolizumab will be administered Q3W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .									
Carboplatin Administration	Carboplatin will be administered Q3W for 4 cycles beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .									Cohort A1 only
Pemetrexed Administration	Pemetrexed will be administered Q3W beginning on Cycle 1 Day 1. Refer to Section 5.1.2 .									Cohort A1 only

^a Refer to [Table 2-6](#) and [Section 5](#) for Follow-Up period

^c [REDACTED] On-treatment biopsy for at least 20 total participants in all dose optimization/expansion cohorts, if clinically feasible. All participants with low risk biopsies (i.e., expected rate of major complications <0.5%, e.g., blood, bone marrow, skin, and superficial masses) must consent and will be required to undergo mandatory pre- and on-treatment biopsies. Moderate risk biopsies (i.e., expected rate of major complications 0.5-1.5%, e.g., intra-abdominal, some intrathoracic, and low risk procedures in patients with increased risk of bleeding or infection) are optional, and not mandatory. High risk biopsies (i.e., expected rate of major complications >1.5%) are not acceptable in this trial based on the current trial objectives.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; C = cycle; CT = computed tomography; D = Day; EOI = end of infusion; EOT = end of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; hCG = human chorionic gonadotropin; IMP = investigational medicinal product; MRI = magnetic resonance imaging; [REDACTED]; Q3W = every three weeks; TSH = thyroid stimulating hormone; WOCBP = women of child bearing potential

Table 2-6: Safety Follow-Up Procedural Outline for All Study Parts (Escalation and Optimization/Expansion)

Procedure	Safety Follow-up ^a			Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 90 Days (± 7 Days)	
Safety Assessments				
Physical Examination	X	X	X	
Vital Signs	X	X	X	Includes body temperature, blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Electrocardiogram	X			12-lead ECG. ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 10.5.1 .
Hematology/Chemistry/ LFTs	X	X	X	Laboratory tests also as clinically indicated; See laboratory assessments in Section 10.5.6 .
Coagulation Profile	X			See Section 10.5.6 .
Thyroid Function Tests	X ^b	X	X	TSH with reflex testing (free T3 and free T4) if TSH is abnormal.
Urinalysis	X	X	X	See Section 10.5.6 .
Pregnancy Test	X	X	X	For WOCBP. Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).
Adverse Event Reporting and Concomitant Medication Assessments				
Monitor for AEs	X	X	X	Non-serious AEs will be collected until 90 days after the last dose of SAR444881, pembrolizumab or cetuximab. AEs should be followed until resolved to baseline, stabilized, or deemed irreversible.
Monitor for SAEs	X	X	X	All SAEs must be collected until 90 days after the last dose of SAR444881, pembrolizumab or cetuximab. See Section 10.2.1 for reporting of SAEs that occur after the safety follow-up period. AEs should be followed until resolved to baseline, stabilized, or deemed irreversible.

Table 2-6: Safety Follow-Up Procedural Outline for All Study Parts (Escalation and Optimization/Expansion)

Procedure	Safety Follow-up ^a			Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 90 Days (± 7 Days)	
Concomitant Medication Assessments	X	X	X	
Sample Collection				
Pharmacokinetic and Immunogenicity /ADA sampling	X	X	X	See Section 10.6 , Section 10.7 , Table 10.5-1 , Table 10.5-2 , Table 10.5-3 , and Table 10.5-4 for the pharmacokinetic and immunogenicity sampling schedule.
Efficacy Assessments				
Body Imaging	See notes			Tumor Assessments should occur every 8 weeks starting from date of first dose (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days) until disease progression, withdrawal of consent, or initiation of another systemic anti-cancer treatment. See Section 10.1.1 for further details.
Bone Scan	See notes			As clinically indicated per local standards. See Section 10.1.1 for further details.
Subsequent Treatments (Anti-cancer)	X	X	X	
[REDACTED]				
[REDACTED]				

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; EOT = end of treatment; hCG = human chorionic gonadotropin; LFTs = liver function tests; MRI = magnetic resonance imaging; [REDACTED]; [REDACTED] (version 2); SAE = serious adverse event; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

^a Follow-up visits at Days [REDACTED] should occur relative to the date of EOT visit

^b Only for Sub-Part 1B participants

■ [REDACTED]

Note: In the event that multiple procedures are required at a single time point, the electrocardiogram (ECG) may be obtained up to 15 minutes earlier or later, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point, ensuring the PK samples can be collected on time.

3 INTRODUCTION AND RATIONALE

3.1 Background

Although existing cancer therapies, including the evolving class of cancer immunotherapeutics, have advanced significantly over recent years, cancer remains the second leading cause of death in the United States (US). More than 1.8 million new cancer cases are expected to be diagnosed in 2020 in the US and about 606,520 Americans are expected to die of the disease, translating to about 1,660 deaths per day [2].

Immunotherapy drugs, which target tumor immune evasion mechanisms, have transformed clinical cancer care, adding a fourth pillar to the historic three pillars of surgery, chemotherapy/targeted agents, and radiotherapy [3]. Immune checkpoint protein inhibitors, such as antibodies against Programmed Cell Death Protein-1 (PD-1), Programmed Death-Ligand 1 (PD-L1) and Cytotoxic T-lymphocyte-Associated Protein-4 (CTLA-4), are now approved in the US for the treatment of multiple cancer types [4, 5]. Unfortunately, the clinical experience accumulated thus far with immune checkpoint blockade has shown that primary tumor refractoriness and acquired tumor resistance prevent the achievement of durable clinical benefit in many patients and so despite the availability of these and other oncology treatment advances, cancer patients with advanced disease continue to represent a patient population with substantial unmet medical needs [6-8]. In addition, the observation that even in immune-responsive tumor types, most patients do not have durable disease control and that for many tumor types, single drug checkpoint inhibitor regimens are ineffective, has led to an interest in developing rational immunotherapy-based combinations that could improve objective response rates or prolong disease control in comparison with monotherapy treatment [9].

SAR444881 is a novel, humanized immunoglobulin G4 (IgG4) monoclonal antibody, that binds to the surface glycoprotein receptor Immunoglobulin-like transcript-2 (ILT2). It is also known as leukocyte Ig-like receptor 1, CD85j, and LILRB1, and is a member of the LILR family of immunomodulating receptors. ILT2 is an inhibitory receptor expressed on monocytes, dendritic cells, natural killer (NK) cells, and B and T lymphocytes [10, 11]. ILT2 has been shown to bind to classical and nonclassical major histocompatibility complex (MHC) class I molecules although its binding affinity to HLA-G is higher than to classical MHC-I molecules. Besides its physiological immunosuppressive role in maternal-fetal tolerance, HLA-G is commonly neo-expressed by solid tumors. It was found to be expressed in multiple tumor types including bladder, cervical, colorectal, gastric, esophageal, liver, head and neck, and lung cancer [12-28]. Expression of HLA-G in patients correlates with clinical parameters such as more advanced disease stage, tumor metastasis and with a worse prognosis [13, 29-31].

The interaction of ILT2 with its ligands MHC-I or HLA-G in the context of an immune reaction can lead to impairment of immune cell proliferation, differentiation, phagocytosis, cytotoxicity, cytokine secretion and chemotaxis; and induction of regulatory cells and myeloid-derived suppressor cells (MDSC) or M2 type macrophages [32-36]. These immunosuppressive effects identify the ILT2 signaling axis as a potential novel target for anti-cancer immunotherapies.

SAR444881 selectively binds to the ILT2 membrane receptor and blocks its interaction with MHC class I and HLA-G molecules expressed by tumor cells. *In vitro* and *ex vivo* studies have demonstrated that SAR444881 enhances macrophage phagocytosis and the cytotoxicity of NK cells and T cells

against multiple types of cancer cells and increases secretion of pro-inflammatory cytokines. In *in vivo* xenograft and humanized mouse models, blocking ILT2 activity with SAR444881 resulted in decreased tumor growth, inhibited metastasis spread and resulted in prolonged survival. In addition, preclinical studies demonstrated an enhanced effect when SAR444881 was combined with approved therapeutics, including epidermal growth factor receptor (EGFR) and PD-1-targeting antibodies.

Based on nonclinical data, treatment with SAR444881 is suggested to prevent ILT2 pathway-mediated inhibition of macrophages, NK and CD8⁺ T-cells, including suppressed anti-tumor immune response of these cells.

3.2 Study Rationale

3.2.1 Scientific Rationale

When properly stimulated, effector cells of both the innate and adaptive immune systems possess the ability to recognize and attack cancer cells [37, 38]. An improved understanding of cancer immune evasion mechanisms has led to the development of immunotherapy drugs, that have transformed the field of oncology in recent years. These novel therapies, which modulate the immune system, now routinely complement conventional chemotherapy, radiation, and targeted therapies in the treatment of cancer patients.

Both adaptive and innate immune cells are endowed with specialized functions to eliminate pathogens, and many of these functions can be redirected against tumors. The emphasis in immunotherapy drug development has been placed so far on drugs that stimulate the adaptive immune system to attack malignant cells, in particular T lymphocytes. This is due to the success of immune checkpoint inhibitors targeting CTLA-4 and the PD-1/PD-L1 axis, which disable inhibitory signals to T cells and generate anti-tumor responses. T lymphocytes-targeting drugs have now been incorporated into the treatment paradigms of multiple tumor types. However, despite the promising results of checkpoint inhibitor treatment, only a subset of patients shows a long-term response and the majority of patients receiving anti-PD(L)1 and anti-CTLA4 therapies do not derive a durable benefit from these novel drugs [3, 8]. Cells of the myeloid lineage are the most abundant immune cells in the body, yet few immunotherapeutic approaches have been aimed at stimulating them to attack cancer. In addition, based on their robust ability to perform phagocytosis and cytotoxicity [39-44], macrophages and NK cells have remarkable potential as targets of anti-cancer immunotherapies. SAR444881, which targets ILT2-expressing NK cells, macrophages, and T cells, may restore the anti-tumor activity of all three immune cell types.

3.2.1.1 The Immunoglobulin-Like Transcript 2 (ILT2) Protein

Ig-like transcript 2 (ILT2), also known as CD85j, LIR-1, and LILRB1, belongs to the human leukocyte Ig-like receptor (LILR) superfamily. The LILR family in turn belongs to the superfamily of paired receptors that contain receptors with the potential to transmit stimulatory or inhibitory signals. In general, these receptors regulate the immune system to temper or augment responses by other cells and mark tolerogenic antigen presenting cells (APCs) [45]. LILR receptors can be classified into two main receptor groups, LILRA and LILRB. LILRB receptors are primate and

human specific and are reported to be predominantly expressed in hematopoietic lineage cells and to suppress activation of various types of immune cells [46].

ILT2 is a 110-kDa surface glycoprotein inhibitory receptor. It is expressed on a wide range of immune cells, including monocytes, dendritic cells, NK, B cells, and T cells, possibly providing inhibitory signals to multiple components of the host's immune system [10, 11, 47-49]. Like other LILRB receptors, ILT2 has four immunoglobulin domains and also contains four immunoreceptor tyrosine-based inhibition motifs (ITIMs) in its cytoplasmic tail that inhibit cellular responses by recruiting SHP-1 [47, 48, 50].

ILT2 recognizes a wide range of both classical and nonclassical MHC-I molecules by interaction with the relatively nonpolymorphic $\alpha 3$ region and the invariant β -2M subunit of class I MHC proteins [33, 48, 49, 51, 52]. It has been shown to recognize HLA-A, -B, -C and -G alleles, however surface plasmon resonance studies suggest that ILT2 binds with a 3- to 4-fold higher affinity to the nonclassical MHC-I molecule HLA-G than to classical MHC-I [11, 53]. HLA-G is predominantly expressed by placental trophoblasts, playing a role in maternal-fetal tolerance, however it is also commonly expressed by solid tumors. HLA-G was found to be expressed in multiple tumor types including bladder, cervical, colorectal, gastric, esophageal, liver, head and neck, and lung cancer [12-28] and its expression correlates with clinical parameters such as more advanced disease stage, tumor metastasis and with a worse prognosis [13, 29-31]. The interaction of ILT2 with its ligands MHC-I or HLA-G in the context of an immune reaction can lead to impairment of immune cell functions such as proliferation, differentiation, phagocytosis, cytotoxicity, cytokine secretion and chemotaxis; and induction of regulatory cells and myeloid-derived suppressor cells (MDSC) or M2 type macrophages [32-36]. These findings identify the ILT2 signaling axis as a potential novel target for reprogramming the immune response, akin to the successful checkpoint blockade strategies employed to restore tumor-specific T cells responses.

In monocytes, phosphorylation of ILT2 results in the binding of the tyrosine phosphatase SHP-1. These phosphatases are known to dephosphorylate signaling effector molecules and prevent or attenuate signaling through immune stimulatory receptors [54-57]. In addition, co-ligation of ILT2 with monocyte's Fc γ receptor I (CD64) was found to inhibit tyrosine phosphorylation of the associated Fc receptor γ chain and Syk molecules, as well as intracellular calcium mobilization, demonstrating that ILT2 inhibits Fc γ RI-induced signaling. These findings suggest that ILT2, which is expressed on a majority of circulating monocytes, functions as a unique MHC class I receptor involved in the inhibition or downmodulation of monocyte activation signals [57]. Several studies have also demonstrated the importance of ILT2 and other LILR family members in regulation of dendritic cells (DCs) activity, suggesting an important role for this family of receptors in establishing activation thresholds and regulating myeloid lineage induction of immune responses [58-62]. ILT2 was found to be involved in maintaining human monocyte-derived DCs in a quiescent state, regulating the capacity of DCs to increase levels of cell-surface antigen presentation and costimulatory molecules, controlling the secretion of cytokines, and influencing T cell reactivity by interacting with a population of regulatory T cells [63].

Studies in NK cells have demonstrated that upon ligand binding, ILT2 is able to inhibit NK cell cytotoxicity [48, 49, 64, 65] and the secretion of IFN- γ [66] and that the inhibitory effect of the

receptor is restored with blocking ILT2 antibodies [49]. Additional studies have demonstrated that ILT2 expressed on primary NK cells is involved in NK cell inhibition via HLA-G [67-69]. The binding of HLA-G to ILT2 up-regulates ILT2 expression in NK cells and the ligand/ILT2 interaction inhibits the polarization of NK cell lytic granules by blocking accumulation of microtubule organizing center and F-actin at the area of contact, intracellular Ca^{2+} mobilization, and IFN- γ production [70, 71].

The ILT2 receptor is also detected in up to 20% of CD3^+ lymphocytes (mostly CD8^+ T cells) [48, 49, 65, 72-74]. Studies using cross-linking of ILT2 and CD3 have shown that ILT2 can inhibit multiple cellular T cell functions including cytokine production and cytotoxicity [65, 72, 75]. Other studies also demonstrated that ILT2 reduces the cytotoxicity of T cells, inhibits production of cytokines that support T cell expansion and function (e.g., IL-2, IFN- γ) and decreases T cells proliferation [76, 77]. ILT2 was found to inhibit CD3/T cell receptor (TCR)-mediated activation in both CD4^+ and CD8^+ clones, and to down-regulate antigen recognition by CD8^+ cells. The inhibitory function of the receptor was also confirmed by its ability to reduce CD3/TCR-induced intracellular Ca^{2+} mobilization [72].

3.2.1.2 Human Leukocyte Antigen (HLA)-G

ILT2 has been shown to bind to HLA-G with a higher affinity than to classical MHC-I molecules [11]. The relatively high affinity of ILT2 binding to HLA-G is consistent with observations that the effects of ILT2-mediated inhibition can be largely attributed to HLA-G recognition.

HLA-G expression was first observed in cytotrophoblasts [78]. Its expression is mainly restricted to the fetal-maternal interface on the extravillous cytotrophoblast, placenta, and amnion where it is thought to confer protection to the fetus from the maternal immune system, thus critically contributing to fetal-maternal tolerance [79-82]. HLA-G expression was also found in erythroid precursors, cornea, thymic medulla, bronchial epithelial cells and pancreatic islets [83-87].

Besides its unique expression on immunologically relevant sites, HLA-G exercises several immunomodulatory activities that could confer immune tolerance to cells that express it [88]. It plays an important role in immunotolerance mechanisms by inhibiting cytolytic functions of NK cells, cytotoxic T-lymphocytes, and T-cell allo-proliferative responses [89]. The immunoinhibitory properties of HLA-G are believed to be beneficial in pregnancy, organ transplantation, and autoimmune disease by promoting uterine implantation of the embryo, accepting solid allografts, and turning down immune reaction against self-components. However, the immunosuppressive effects become deleterious in cancer and viral infections by allowing tumor cells and viruses to evade antitumor or antiviral responses [13, 90].

By binding receptors expressed on immune cells, HLA-G directly inhibits the functions of NK cells, cytotoxic T-lymphocyte (CTLs), B cells, neutrophils and DCs [29]. HLA-G-mediated inhibition of innate and adaptive cells depends on cell types and the profiles of HLA-G receptors they express; identified HLA-G receptors include ILT2, ILT4, KIR2DL4 and CD160 [31].

The direct immunosuppression effect induced by HLA-G includes inhibition of CTL and NK cell lysis, inhibition of cytolytic functions of CD8^+ T cells, inhibition of allogeneic CD4^+ T-cell proliferation, general proliferation blockade of $\text{T}_{\alpha/\beta}$ cells in G1 phase, and the induction of apoptosis of CD8^+ T and NK cells [91-94]. HLA-G also affects DCs maturation, migration, trafficking, antigen

presentation and their crosstalk with T and NK cells, and inhibits V γ 9V δ 2 T-cell proliferation and IFN- γ production and cytotoxicity; these effects were shown to be mediated by interacting with the ILT2 receptor [31, 95-98]. HLA-G was also found to have indirect immunoregulatory activities by inducing tolerogenic cells including T regulatory (Treg) cells, CD4^{low} and CD8^{low} suppressor T cells, MDSC and tolerogenic DCs (DC-10) [99-101].

Soluble HLA-G (sHLA-G) was also found to have the potential to modulate the immune response. It was demonstrated to inhibit B-cell proliferation, differentiation and immunoglobulin secretion in both T-cell-dependent and -independent models of B-cell activation through the ILT2 receptor [102]. sHLA-G also impairs expression and function of different chemokine receptors in T cells, NK cells and B cells through ILT2 and modulates migration of peripheral blood NK cells [36, 103].

3.2.1.3 ***ILT2 and HLA-G Expression and Role in Cancer Pathogenesis***

One strategy used by tumor cells to escape innate and adaptive immune responses is associated with an induced aberrant expression of molecules that activate immunosuppressive pathways. One possible tumor evasion mechanism is expression of HLA-G, known to bind and activate the ILT2 receptor [31, 104].

The interactions between ligands and LILRB receptors are proposed to serve as immune checkpoints. Upon stimulation by ligands, such as HLA-G expressed on tumor cells, LILRBs inhibit immune activation thus indirectly supporting tumor development [46]. Recent data support the MHC class I–ILT2 signaling axis being an important regulator of the effector function of innate immune cells, such as macrophages and NK cells, and a potential target of anti-cancer immunotherapies [33]. Published data highlight the role of the ILT2 pathway in the evasion of tumor cells from an immune response [105].

ILT2 was shown to generate a “don’t eat me signal” in macrophages resulting in reduced elimination of tumor cells [33, 105]. Expression of the common MHC class I component β 2-microglobulin (β 2M) by cancer cells directly protected them from phagocytosis. Protection from phagocytosis was found to be mediated by the ILT2 receptor, whose expression was upregulated on the surface of macrophages, including tumor-associated macrophages. Modifying the expression of ILT2 in human macrophages using CRISPR–Cas9 demonstrated a significantly greater phagocytic ability of ILT2-null macrophages. Disruption of either ILT2 or MHC class I potentiated phagocytosis of tumor cells by macrophages both *in vitro* and *in vivo* [33]. Deletion of ILT2 from macrophages results in a significantly greater abundance of macrophages with an ‘anti-tumor’, M1-like surface profile demonstrating a potential role for the receptor in the development of an anti-inflammatory/‘pro-tumor’ tumor microenvironment (TME) [33].

NK cells from cancer patients display altered receptor signatures that may prevent them from developing their full range of potential anti-tumor activities. Studies in breast cancer have demonstrated that ILT2 is involved in the regulation of NK cells’ anti-tumor activity. In a cohort of breast cancer patients, the expression of ILT2 on NK cells increased with the progression of breast cancer with concomitant decrease in functions of NK cells [106, 107]. Blockade of ILT2 was shown to restore the cytotoxicity function of NK cells against tumor cells in triple negative breast cancer

[107].

The ability of ILT2 to inhibit cytolytic functions could render tumor-specific T lymphocytes unable to recognize tumor cells, thus providing an escape mechanism that may favor cancer development [72]. ILT2 expression was demonstrated to be significantly elevated in CD4⁺ and CD8⁺ T cells of metastatic melanoma patients compared to healthy donors and a low frequency of CD8⁺ILT2⁺ T cells at baseline appeared to be highly predictive of clinical response to an oncolytic virus immunotherapy [108]. ILT2 was also shown to be specifically expressed in intra-tumoral CD8 T cells in several tumor types, including hepatocellular carcinoma, NSCLC, and colorectal cancer [109]. Recently, ILT2 was found to be expressed by a specific sub-population of CD8⁺ T cells commonly found in TMEs (T_{EMRA}, effector memory T cells re-expressing CD45RA). The ILT2⁺ CD8 T_{EMRA} sub-population, which expresses effector molecules such as perforin and granzymes, is distinct from PD-1-expressing CD8⁺ T cells suggesting different roles of the two receptors in regulating the antitumor response [109].

A strong correlation between ILT2 expression in peripheral CD8 T cells and recurrence of non-muscle invasive bladder (NMIBC) cancer was observed. The survival of NMIBC patients with low levels of ILT-positive CD8 T cells was significantly prolonged [110]. ILT2 was also found to be upregulated in esophageal cancer and various adenocarcinomas including gastric and colorectal and the expression of ILT2 was inversely correlated with survival [111, 112].

Together, the data suggest that ILT2 functions as a negative regulator of human CD8⁺ effector T cells and that blocking ILT2 represents a unique strategy to enhance the anti-tumor activity of T cell-targeting immunotherapeutics.

The Sponsor has evaluated the expression of ILT2 in cancer. When examining ILT2 expression in single cell suspensions generated from tumor samples of NSCLC, RCC, esophageal, CRC, and H&N cancer patients, ILT2 was found to be expressed in 20% of the total immune cell population inside the TME. ILT2 was expressed in more than 80% of monocytes (CD14⁺ myeloid cells) and macrophages, and in more than 50% of NK cells. Lower expression levels were observed in overall CD4 and CD8 T cell population. However in CD8 T cells, ILT2 was found to be expressed at higher levels in PD-1-negative T_{EMRA} cells; a sub-population of CD8⁺ lymphocytes known to be found in the TME and to be upregulated following anti-PD-1 therapy [113].

Similar results were observed in bioinformatic analysis of RNAseq data from the TCGA database. In a Gene-Set Enrichment Analysis (GSEA) bioinformatic analysis of the TCGA database using the TCIA (Cancer Immunome Atlas) (www.tcia.at), a correlation was observed between higher expression levels of ILT2 and enrichment of both suppressive MDSC and M2 cells in the TME of cancer patients. When examining enrichment of T_{EMRA} CD8 T cells across the TCGA, 22.8-47.3% of patients were found to have high T_{EMRA} levels. Analysis of ILT2 levels in patients with high T_{EMRA} levels found that 57-94% had high levels of ILT2 indicating an association between ILT2 and T_{EMRA} levels.

HLA-G, expressed on malignant cells, can interact with ILT2 expressed on various types of immune cells and impair the function of host immune effector cells, enabling tumor immune evasion. *In vitro* studies with cell lines of ovarian carcinoma, hepatocellular carcinoma, glioma, melanoma and renal cell carcinoma demonstrated that upon expression of endogenous HLA-G, tumor cells were protected from lysis by alloreactive NK cells and lymphokine-activated killer cells and/or antigen-specific

CD8⁺ T cells. This protective effect could be reversed by masking HLA-G antigens using HLA-G or its receptor-specific antibody including an ILT2-specific mAb [68, 114-116]. *In vivo* studies have demonstrated that human or murine tumor cells expressing HLA-G can grow in immunocompetent host mice and that blocking HLA-G function by a specific antibody inhibits the development of tumors. The *in vivo* studies also demonstrated that HLA-G could impair both innate and adaptive immunity resulting in an expansion of myeloid-derived suppressor cells, loss of peripheral T cells and a cytokine balance in favor of a Th2 profile [32, 117].

HLA-G was reported to render tumor cells with a higher invasive, metastatic potential, indicating that its expression has multiple effects including promoting tumor cells escape from immune surveillance and enhancing their metastasis during the progression of malignancies [32, 46, 114, 117, 118]. HLA-G expression was found to have multiple effects supporting the progression of malignancies. These effects include inhibiting cytolytic functions of CD8⁺ T cells, T γ / δ cells, and NK cells, inducing immune cell apoptosis, generation of inhibitory regulatory cells through receptor binding and/or trogocytosis, and impairing chemotaxis of different immune effector cells through modulation of cytokine, e.g. IL-10, and chemokine secretion. Furthermore, tumors induce HLA-G expression by other cells, such as myeloid APCs, resulting in an indirect tumor inhibitory effect on T and B lymphocytes [30, 36, 82]. V γ 9V δ 2 T cells play a crucial role in the antitumoral immune response through cytokine production and cytotoxicity. Soluble HLA-G inhibits V γ 9V δ 2 T-cell proliferation and production of IFN- γ [46, 98].

Since the initial report of HLA-G expression in melanoma, its expression has been studied in multiple types of tumors, where HLA-G expression was observed on tumor cell surface, secreted or in tumor-derived exosomes but not in normal surrounding tissue [30, 31, 82, 119]. Using immunohistochemical assays, HLA-G was found to be expressed in bladder, cervical, colorectal, gastric, esophageal, liver, head and neck, and lung cancer [12-28]. Expression of HLA-G in patients was found to be correlated with clinical parameters such as more advanced disease stage, tumor metastasis or with a worse prognosis [13, 29-31]. In addition to tumor tissue expression, soluble HLA-G (sHLA-G) levels have also been reported to be increased in patients with melanoma, neuroblastoma, lymphoproliferative disorder, and breast and ovarian cancer [120-125]. Neuroblastoma patient sera selected according to high sHLA-G concentrations inhibited NK cell and cytotoxic T lymphocytes-mediated neuroblastoma cell lysis. Such lysis was partially restored by serum depletion of sHLA-G demonstrating that sHLA-G dampens anti-tumor immune responses [125].

Besides being correlated with advanced disease stage and poorer patient outcome, sHLA-G was also found to be a potential biomarker of clinical outcomes in cancer patients treated with immunotherapies. Non-small cell lung cancer (NSCLC) patients, who displayed disease progression when treated with the PD-1 blocker nivolumab, were found to have higher baseline sHLA-G levels compared to patients who achieved a Partial Response or Stable Disease [126]. In addition, patients with prolonged survival had lower sHLA-G indicating a possible effect of HLA-G on patient response to approved immunotherapies. High peripheral sHLA-G was also found to be negatively correlated with CD3/CD8⁺ T-cell tumor microenvironment infiltration, further supporting its possible immunosuppressive effect.

The Sponsor has evaluated the expression of HLA-G in several tumor types by immunohistochemistry (IHC) of tissue microarrays [127, 128]. An IHC score was developed based on staining intensity and number of stained cells and a score above 100 was considered to represent high expression of HLA-G. High HLA-G expression was found in 37% to 55% of esophageal, H&N, microsatellite stable (MSS) colorectal, and gastric cancer patients. In normal tissues, only minimal expression of HLA-G was observed.

3.2.2 Summary of SAR444881 Nonclinical Data

A detailed description of SAR444881 pharmacology, toxicology and pharmacokinetics is provided in the SAR444881 Investigator's Brochure.

3.2.2.1 Nonclinical Experience (In Vitro and In Vivo)

SAR444881 is a humanized IgG4 isotype mAb with L235E/S228P mutations that diminish its binding to Fc γ receptors (Fc γ R) and prevent Fc γ R-mediated activation of innate immune effector cells. SAR444881 was demonstrated not to induce antibody-dependent cell-mediated cytotoxicity (ADCC) and does not bind the complement component C1q and therefore is not expected to induce complement-dependent cytotoxicity (CDC).

SAR444881 binds human ILT2 with high affinity [REDACTED] and is highly selective to ILT2 compared to other ILT (LILR) receptors. *In vitro* functional data demonstrate that it is a potent blocker of intercellular ILT2-HLA-G and ILT2-MHC-I interactions.

SAR444881 was shown *in vitro*, *ex vivo* and *in vivo* to enhance the anti-tumor activity of innate and adaptive immune cells.

SAR444881 increases the phagocytosis of target tumor cells by macrophages, including tumor cells isolated from patients with several tumor types. In contrast, SAR444881 was found not to enhance phagocytosis of non-target cells (human normal hepatocytes) by macrophages. SAR444881 was also found to enhance the anti-tumor activity of NK cells. SAR444881 was shown to enhance the direct cytotoxicity, membranal CD107a expression and IFN γ and granzyme B secretion by NK cell line cells and primary NK cells in the presence of target cancer cells. The increase in CD107a and IFN γ expression was found to correlate with ILT2 expression on NK cells. In addition, SAR444881 was shown to reverse ILT2-mediated inhibition of NK cells by restoring the phosphorylation signal of Syk. *In vitro*, SAR444881 enhances the anti-tumor activity of T cells – SAR444881 was shown to restore T cell activity inhibited by ILT2-mediated signaling when studied in IL-2 secretion assays. In addition, SAR444881 was shown to reverse ILT2-mediated inhibition of T cells by restoring the phosphorylation signal of ZAP70.

SAR444881 displays potent anti-tumor activity in tumor xenograft *in vivo* models. In preventive and established melanoma lung lesion mouse models SAR444881 inhibited tumor growth by [REDACTED]. In a colorectal xenograft mouse model engrafted with macrophages, tumor growth was inhibited by [REDACTED] with prolonged survival observed in SAR444881-treated mice. When evaluating the activity of SAR444881 in a Head & Neck cancer humanized mouse model, complete responses were observed in 2/4 mice. SAR444881 administration *in vivo* was demonstrated to increase levels of activated T and NK cells within tumors as shown by the higher frequency of cells expressing CD107a and CD69. The effect of SAR444881 was also found to correlate with a shift in the M1/M2 ratio of tumor-

associated macrophages. These results demonstrate the potential of SAR444881 [REDACTED]
[REDACTED]
[REDACTED]

Preclinical models also demonstrated an enhanced SAR444881 effect when combined with approved therapeutics. SAR444881-enhanced phagocytosis of EGFR⁺ tumor cells *in vitro* was further augmented when combined with tumor-targeting antibodies such as cetuximab. [REDACTED]
[REDACTED]
[REDACTED]

3.2.2.2 Nonclinical Safety Pharmacology and Toxicology

Preclinical evaluation of the safety of SAR444881 included assessment of the effect of SAR444881 on T cell proliferation and pro-inflammatory cytokine secretion. Human peripheral blood mononuclear cells (PBMCs) from 10 healthy donors were evaluated and the antibody was presented by both soluble and immobilized form. There was no apparent SAR444881-induced proliferation and no significant pro-inflammatory cytokine secretion in soluble or dry-coated immobilized stimulation formats. Similar preclinical studies conducted with SAR444881 in combination with anti-PD-1 blocking antibodies and with anti-EGFR antibodies also demonstrated no apparent T cell proliferation and no significant pro-inflammatory cytokine secretion.

A 4-week Good Laboratory Practice (GLP) repeat dose study was performed in Cynomolgus monkeys to evaluate the toxicity and toxicokinetics of SAR444881. SAR444881 was administered via IV infusion once a week for a total of 5 doses at doses representing 1X (10mg/kg), 5X (50 mg/kg) and 10X (100 mg/kg) the projected maximal dose in humans (10 mg/kg). SAR444881 was well tolerated with no obvious treatment related adverse effects, no gross or microscopic treatment related pathological findings, and no mortality observed. Ophthalmological evaluation and electrocardiography indicated no findings related to the treatment. In addition, all blood and urine tests were found to be within normal ranges for Cynomolgus monkeys. There was no apparent SAR444881 -induced pro-inflammatory cytokine secretion. Taken together, the pivotal GLP repeat-dose toxicology study in Cynomolgus monkeys showed no treatment-related toxicities at any dose level, and the No Observed Adverse Effect Level (NOAEL) was determined to be 100 mg/kg.

In a GLP-compliant tissue cross-reactivity study SAR444881-stained membrane and cytoplasm of resident, migrating, and/or infiltrating mononuclear cells in several human tissues. The staining of mononuclear cells in the human tissues with SAR444881 is consistent with the expression of its target protein, ILT2, by monocytes/macrophages, lymphocytes, and dendritic cells.

Staining with SAR444881 was also observed in epithelial cells in pancreas and small intestine in human tissues. All observed staining was cytoplasmic in nature and was judged to be of little to no toxicologic concern due to the limited accessibility of the cytoplasmic compartment to monoclonal antibodies *in vivo*. Off target binding or potential for organ toxicity were not identified. This is also corroborated with the results of the safety toxicology study in Cynomolgus monkeys.

3.2.2.3 Nonclinical Pharmacokinetics

The Toxicokinetic (TK) evaluation of SAR444881 in Cynomolgus monkeys was performed as part

of the preliminary tolerability and TK study as well as in the GLP repeat dose toxicity study. These studies utilized SAR444881 material from the toxicology run, that is representative of the manufacturing process and quality attributes of the clinical material. Serum SAR444881 was measured in the monkeys using a validated procedure.

Overall, the kinetics of SAR444881 in the monkeys was typical for monoclonal antibodies. Following intravenous infusion, the serum concentrations of SAR444881 declined in bi-phasic fashion: after the distribution phase, the SAR444881 serum concentrations declined more slowly, over the time course of days and weeks. There was no apparent change in the kinetics of SAR444881 elimination at the lower concentrations (in the post-distributional phase), and no evidence of target-mediated drug disposition (TMDD) of SAR444881 in the monkeys at the investigated doses. The average terminal half-life of SAR444881 was [REDACTED] days for the [REDACTED] mg/kg dose.

The toxicokinetics evaluation of the GLP study in Cynomolgus monkeys showed a dose-proportional increase in SAR444881 exposure (C_{max} , AUC) when administered by IV infusion, with an increase in C_{max} and AUC on Day 29 (after 5th dose) as compared to Day 0, which might suggest the potential for some SAR444881 accumulation with a repeated dosing regimen.

Taken together, the values of the pharmacokinetic parameters obtained in the non-compartmental analysis of SAR444881 concentration vs. time as well as the values of the terminal half-life and the clearance of SAR444881 are characteristic to monoclonal antibodies that undergo FcRn-mediated recycling.

3.2.3 Combining ILT2 blockade with PD-1 blockade and an anti-EGFR tumor targeting antibody

Immune checkpoint blockade, like anti-CTLA-4, PD-1 and PD-L1 antibodies, promotes T-cell mediated cancer cell death by enhancing host immune responses to tumors. However, intrinsic cancer and host factors can influence and hamper anti-cancer immune responses and only a subset of patients derive significant clinical benefit with single agent anti-CTLA-4 or anti-PD-1 antibodies. Thus, combinations of immunotherapy agents solely or combined with known active anticancer treatments have been developed to improve patients' clinical outcomes [129].

TCD17465 will also study SAR444881 in combination with other therapeutics. The Sponsor has demonstrated in preclinical studies that the anti-tumor effect of SAR444881 was augmented when combined with the tumor-targeting antibody cetuximab, and when combined with an approved PD-1 blocking antibody. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.2.3.1 SAR444881 in Combination with Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (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 PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical

development as an intravenous (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 Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [130]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma [131, 132].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (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) [133, 134].

The structure of murine PD-1 has been resolved [135]. PD-1 and the other receptors in this family are type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) extracellular domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules [135]. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the highly related 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 [134, 136-138]. The mechanism by which PD-1 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 [139, 140]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCLC, GC/GEJ, and HNSCC.

Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/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 [141-146]. Anti-mouse PD-1 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 [135, 144, 146, 147]. 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 PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [146]. Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models.

Data Supporting Combining Pembrolizumab with SAR444881

Preclinical ILT2 data and clinical data of approved and investigational immunotherapy drugs targeting lymphocyte and macrophage inhibitory receptors support combining SAR444881 with PD-1 blocking antibodies such as pembrolizumab.

The Sponsor has demonstrated in preclinical studies that ILT2 and PD-1 are expressed by different populations of CD45⁺ PBMCs supporting the complementing effect that targeting the two immune inhibitory receptors might have. The data is supported by published research confirming that ILT2 is expressed by effector memory T cells re-expressing CD45RA (T_{EMRA}), a sub-population of CD8⁺ T cell which is distinct from PD-1-expressing CD8⁺ T cell populations. In addition, PD-1 blockade was found to upregulate ILT2 expression by tumor infiltrating lymphocytes, possibly because of increased IL-2 production by T cells, and to upregulate levels of T_{EMRA} cells, which are known to express ILT2. These data suggest different roles of the two receptors in regulating the antitumor response and that the combination of ILT2 and PD-1 blockade may enhance the tumoricidal activity of CD8⁺ T cells compared to PD-1 blockade alone. Engaging ILT2 with its ligand HLA-G on tumor cells significantly inhibited bispecific T-cell engager (BiTE) molecule-induced CD8⁺ T cell activation. Blocking ILT2 and PD-1 induced greater CD8⁺ T cell activation than either treatment alone in *in vitro* solid tumor models [109, 113, 148-150]. The nonoverlapping expression of ILT2 and PD-1 in tumor-infiltrating CD8⁺ T cells was observed by single-cell RNAseq analysis in several tumor types, including hepatocellular carcinoma, NSCLC, and colorectal cancer [151-153]. Finally, higher baseline levels of soluble HLA-G, ILT2 receptor's activating ligand, were found to be associated with reduced response and shorter survival in non-small cell lung cancer patients treated with an anti-PD-1 [126] further demonstrating that the HLA-G-ILT2 pathway may represent a resistance mechanism to PD(L)-1 blockade therapy.

These data further support targeting the HLA-G-ILT2 inhibitory pathway as a strategy to enhance the efficacy of drugs targeting the PD-L1-PD-1 tumor immune evasion mechanism. The potential additive effect of combining SAR444881 and pembrolizumab is expected both by the ability of this therapeutic combination to activate two different CD8⁺ T cell subsets and the potential for anti-PD(L)-1 therapy to increase differentiation and accumulation of ILT2⁺ effector T cells, whose activity would be potentiated by ILT2 blockade.

Combining two immunotherapies targeting lymphocyte checkpoint inhibitors with complementing and non-redundant mechanism of actions has been evaluated in several tumor types demonstrating an improved benefit [9]. CTLA-4 acts as an immune checkpoint during the early stages of T cell activation predominantly in subsets of Th1-like CD4⁺ effector T cells, while PD-1 attenuates T-cell receptor signaling during later stages and primarily suppresses subsets of CD8⁺ T cells [154]. The combination of nivolumab, an anti-PD1 mAb, and ipilimumab, an anti-CTLA-4 mAb, has

demonstrated clinical efficacy and has been approved for the treatment of advanced melanoma, renal cell carcinoma, malignant pleural mesothelioma, non-small cell lung cancer, colorectal cancer, and hepatocellular carcinoma [155]. Combinations of PD-1 and PD-L1 inhibitors with other inhibitory molecules, such as inhibitors of LAG3, T-cell immunoglobulin and mucin domain containing molecule 3 (TIM-3), V domain containing Ig suppressor of T-cell activation, and TIGIT, are also actively being pursued.

Emerging clinical data supporting the combination of PD-1 blockade and macrophage checkpoint inhibitors has recently been reported. ALX148, a fusion protein that blocks the CD47-mediated immunosuppressive signal and enhances macrophage anti-tumor immunity and cross priming of T cells, is being studied in combination with pembrolizumab for the treatment of solid tumors [156, 157]. Combining ALX148 with pembrolizumab in 20 squamous cell carcinoma of the head and neck (SCCHN) patients progressing on prior chemotherapy resulted in an ORR of 20% and a DCR of 30%. In checkpoint inhibitor naïve patients, the ORR was 40% and the DCR 50% and the reported median OS was 22.1 months. Initial data demonstrating anti-cancer activity, including complete and partial objective responses, of ALX148 in combination with pembrolizumab and chemotherapy in SCCHN patients was also reported.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.2.3.2 SAR444881 in Combination with Cetuximab

Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the epidermal growth factor receptor (EGFR) [158, 159]. The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor- α . *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR.

Cetuximab has demonstrated clinical benefit as a single agent and in combination with chemotherapy and with radiation therapy. It is currently approved as a single-agent and as part of a combination regimen for the treatment of advanced SCCHN. Cetuximab is also approved for the treatment of K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer in combination with chemotherapy and as a single-agent.

NK cells are the primary effectors of ADCC and thus may play an important role in antibody-based therapies, such as cetuximab, approved for the treatment of cancer [160]. NK cells have a role in the effectiveness of monoclonal antibodies targeting tumor antigens by eliminating antibody-coated tumor cells. NK cells in the peripheral blood of cancer patients show overexpression of the ILT2 inhibitory receptor. Patients expressing high levels of ILT2 were found to have an impaired ability to lyse cancer cells in the presence of cetuximab and functional blockade with an ILT2 antagonist antibody restored ADCC levels and reverted the observed negative effect [106, 107]. Natural Killer Group 2A (NKG2A) is an inhibitory receptor expressed on NK, $\gamma\delta$ T cells, and tumor infiltrating CD8⁺ T cells – combining NKG2A blockade with cetuximab had an additive effect on anti-tumor immunity *in vitro*, enhancing NK cell-mediated ADCC against SCCHN tumor cells [161]. These data suggest that strategies that overcome ILT2-driven immune inhibition could improve the clinical efficacy of cetuximab, presenting a rational for combining SAR444881 with antibodies that generate an anti-tumor effect via ADCC.

Drugs targeting inhibitory NK cell receptors have been studied in clinical trials in combination with tumor targeting antibodies. Monalizumab is a humanized IgG4 targeting NKG2A. The NKG2A inhibitory receptor binds to HLA-E molecules that are frequently upregulated on cancer cells and provides a negative regulatory signal to tumor infiltrating lymphocytes (TILs). Monalizumab blocks the binding of NKG2A to HLA-E, and thereby enhances NK and T cell-mediated anti-tumor responses. Clinical studies have shown a potential benefit of combining NKG2A blockade with cetuximab [161-163]. The safety and efficacy of monalizumab in combination with cetuximab was studied in a Phase 2 clinical trial in patients with previously treated SCCHN. Combining the two drugs resulted in an ORR of 27.5% in 40 evaluable patients, a median PFS of 4.5 months and a median OS of 8.5 months, which compare favorably with historical data for single agent cetuximab. Responses were observed in patients who had previously received immunotherapy. These data suggest that strategies that overcome ILT2-driven immune inhibition could improve cetuximab's clinical efficacy.

Tumor-binding antibodies, such as trastuzumab and cetuximab, exhibit multiple modes of action, and their efficacy is linked, in part, to their ability to stimulate antibody-dependent cellular phagocytosis (ADCP) of cancer cells [164]. However, the potency of this response is dampened by the expression on the surface of cancer cells of regulatory proteins which engage inhibitory receptors on macrophages and function as an anti-phagocytic signals [165, 166].

CD47 is a “do not eat me,” antiphagocytic signal that is overexpressed by multiple cancer types to enable the immune evasion from macrophages and other phagocytes. Anti-CD47 antibodies can induce phagocytosis of tumor cells by the blockade of CD47 and its ligand SIRP α and clinical studies have shown a potential benefit of combining CD47 blockade with tumor-binding antibodies [156, 157, 162, 163, 167, 168]. ALX148 is a fusion protein with a high affinity CD47 blocker linked to an inactive human immunoglobulin Fc region that blocks the CD47-mediated immunosuppressive signal and enhances macrophage anti-tumor immunity. In a first-in-human Phase 1 trial, ALX148

was studied in combination with established anticancer antibodies. In HER2⁺ gastric/gastroesophageal junction cancer patients who have progressed on prior chemotherapy, ALX148 in combination with the anti-HER2 antibody trastuzumab had an ORR of 21.1% (19 evaluable patients), with a median duration of response of 8.7 months and median OS of 8.1 months. Combining ALX148 with trastuzumab, ramucirumab, and paclitaxel in advanced gastric cancer patients resulted in an ORR of 64.3% further demonstrating initial anti-tumor activity of macrophage checkpoint inhibitors in combination with tumor antigen targeting antibodies.

Magrolimab, an anti-CD47 antibody that blocks the macrophage CD47-SIRPα inhibitory axis, has been studied in combination with rituximab, an anti-CD20 antibody. Rituximab induces complement and NK cell mediated ADCC effects and provides a potent phagocytic signal for macrophages by stimulating ADCP. Combining rituximab and magrolimab showed promising activity in patients with aggressive and indolent lymphoma in early-stage clinical studies. In a Phase 1b study of magrolimab in combination with cetuximab, objective responses were observed in 2 out of 32 KRAS wild type evaluable colorectal patients; the disease control rate was 50%.

In preclinical studies, SAR444881 -enhanced phagocytosis of EGFR⁺ tumor cells was further augmented when combined with cetuximab. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In Part 2 of the study, cetuximab is proposed for use in combination with SAR444881 in CRC and NSCLC. Cetuximab is widely utilized in first and later line EGFR-expressing CRC that are wildtype for *K-* and *N-RAS* [169]. Cetuximab-containing regimens are not usually recommended for treatment of *RAS* mutant tumors since these mutations are often associated with cetuximab resistance. However, it has been demonstrated that cetuximab-mediated ADCC activity is correlated with the cell surface expression level of EGFR but not with the *KRAS/BRAF* mutational status in colorectal cancer [170], with ADCC (and ADCP) remaining intact in patients with tumors harboring these mutations. Given that we have demonstrated that the combination of SAR444881 with cetuximab enhances ADCC/ADCP, we are therefore proposing to include *KRAS/BRAF* mutant patients in the CRC optimization/expansion cohort (Cohort C1).

Regarding NSCLC, cetuximab is not approved for use in this indication despite multiple Phase 3 trials showing a marginal but statistically significant benefit from cetuximab treatment (reviewed in [171]). The majority of studies of cetuximab in NSCLC have focused on combinations with chemotherapy (e.g., [172], [173], [174]) and although an absolute survival benefit was observed in unselected populations, these regimens have thus far been deemed unjustifiable due to combinatorial toxicity. As is the case in CRC, the aim of testing the SAR444881 combination with cetuximab in NSCLC in Part 2 (Cohort E1) is to leverage the ADCC/ADCP promoting properties of cetuximab as opposed to disrupting the interaction between EGFR and its ligand, EGF. It is for this same reason that NSCLC patients harboring driver mutations will be eligible for enrollment in Cohort E1. Finally, given the safety profile exhibited by SAR444881 to date, both as a monotherapy and in combination with cetuximab (see Section 3.2.4), it is anticipated that lower toxicity will be observed with a SAR444881/cetuximab regimen as opposed to a cetuximab/chemotherapy regimen.

As of 14 January 2024, there have been 76 participants enrolled in TCD17465. 31 participants were enrolled in Part 1A in 6 dose levels of SAR444881 (0.1, 0.3, 1, 3, 10, and 20 mg/kg on a Q2W schedule), 23 participants in Part1B in 4 dose levels (1, 3, 10, and 20 mg/kg) and 22 participants in Part 1C in 4 dose-levels (1, 3, 10, and 20 mg/kg). Q3W and a Q2W dosing regimens were used for Sub-Parts 1B and 1C, respectively.

No [REDACTED] or any new safety signal have occurred in the monotherapy or in any of the combination cohorts as of the cut-off date. For more detailed information regarding safety please refer to the Investigator's Brochure.

It is anticipated that SAR444881 administered as a single agent and in combination with pembrolizumab or with cetuximab will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support its further clinical testing as a treatment for solid tumors.

Immunotherapy drugs, which target tumor immune evasion mechanisms, have transformed clinical cancer care. Immune checkpoint protein inhibitors, such as antibodies against PD-1, PD-L1 and CTLA-4, are approved for the treatment of multiple cancer types [4, 175]. Unfortunately, the clinical experience with immune checkpoint blockade has shown that primary tumor refractoriness and acquired tumor resistance prevent the achievement of durable clinical benefit in many patients and so despite the availability of these and other oncology treatment advances, cancer patients with advanced disease continue to represent a patient population with substantial unmet medical needs [6-8]. Combinations of immune checkpoint inhibitors with other therapeutics, such as other immunotherapies, chemotherapy or targeted therapies, have shown encouraging clinical benefit characterized by enhanced antitumor effects and tolerable safety profiles and are now approved for the treatment of multiple solid tumor types [5, 9, 129, 155].

SAR444881 is a novel IgG4 monoclonal antibody, that binds to the immune inhibitory ILT2 receptor

and blocks its interaction with MHC class I and HLA-G molecules. *In vitro* and *ex vivo* studies have demonstrated that SAR444881 enhances macrophage phagocytosis and the cytotoxicity of NK cells and T cells against multiple types of cancer cells and increases secretion of pro-inflammatory cytokines. In *in vivo* solid tumors mouse models, blocking ILT2 activity with SAR444881 resulted in decreased tumor growth, inhibited metastasis spread and resulted in prolonged survival. Preclinical studies also demonstrated an enhanced anti-tumor effect when SAR444881 was combined with the tumor-targeting antibody cetuximab and when combined with a PD-1 blocking antibody.

Based on preclinical data, administration of SAR444881 may prevent ILT2 pathway-mediated inhibition of macrophages, NK cells and T lymphocytes, including the anti-tumor immune response of these cells. The development of SAR444881 may present an opportunity to assess the effect of a novel checkpoint inhibitor that targets multiple types of effector immune cells, resulting in a potentially broader anti-tumor immune activation compared to other checkpoint inhibitors. Consistent with currently approved checkpoint inhibitors and data from clinical trials of other immunotherapies, a broad immune response mediated by both adaptive and innate immune cells may lead to a clinical benefit in cancer patients supporting the evaluation of SAR444881 as a potential cancer therapy as a single agent regimen and in combination with other therapeutics.

Study TCD17465 is the first-in-human study of SAR444881. It is an open-label, multicenter, dose escalation and optimization/expansion study designed to evaluate the safety and tolerability of SAR444881 administered as a single agent and in combination with pembrolizumab or with cetuximab. The study also aims to evaluate the preliminary anti-tumor activity of SAR444881 monotherapy and collect additional data that will inform future clinical development – the study is designed to also characterize the PK profile of SAR444881 and to explore potential associations between anti-tumor activity of SAR444881 and select biomarker measures in the tumor and peripheral blood. Future studies will evaluate preliminary anti-tumor activity of SAR444881-based combinations. TCD17465 will enroll advanced cancer patients with unresectable or metastatic disease who are refractory to or are not candidates for standard approved therapy and so focuses on patient populations with substantial unmet need for novel cancer treatments.

The study will be comprised of two parts – an initial SAR444881 dose escalation design, chosen to establish a safe and tolerated dose of SAR444881 when administered alone and in combination, followed by a dose optimization/expansion phase studying SAR444881 monotherapy and combination therapy in select solid tumor types known to express the non-classical MHC class I molecule HLA-G. The primary objectives of the dose escalation part of the study are to assess the safety and tolerability of SAR444881 and determine the maximum tolerated dose (MTD) (or Maximum Administered Dose (MAAD), if no MTD is reached) and the recommended dose(s) of SAR444881 when administered alone and in combination with pembrolizumab or with cetuximab that will be used in the dose optimization/expansion part and subsequent clinical trials. In the escalation part, escalating doses of SAR444881 will be administered following a standard “3 + 3” escalation design with dose level cohorts enrolling at least three participants. Pembrolizumab, cetuximab, pemetrexed, and carboplatin will be administered at their recommended dosage. The main advantages of the traditional “3+3” design are that it is simple to implement and considered safe [176]. In addition, the accrual of three participants per dose level provides additional information about pharmacokinetic interpatient variability. As a safety measure, the SAR444881 dose in

combination cohorts will be escalated to a higher dose level only after the higher dose was determined to be safe in the corresponding single agent dose escalation cohort.

The proposed SAR444881 starting dose of 0.1 mg/kg is based on the Minimal Anticipated Biological Effect Level (MABEL) as determined in *in vitro* studies on human cells. The starting dose is anticipated to result in low biological activity and has been calculated to provide a predicted human systemic exposure at the level of the effective concentration that induced 20-50% of the maximal effect observed in *in vitro* tumor models. For additional details see [Section 3.2.7](#). In the Cynomolgus monkeys GLP toxicology study SAR444881 was well-tolerated with no treatment-related toxicities at doses up to ■■■ mg/kg. The starting dose and escalation scheme of the dose escalation phase were selected to assure a balance between the safety of participants, particularly at the first clinical dose administered, and the desire for efficient dose escalation to reach therapeutically active doses.

The primary objective of the dose optimization/expansion part of the study is to assess preliminary anti-tumor activity of SAR444881 monotherapy and combination therapy with pembrolizumab or with cetuximab and/or chemotherapy, and to determine the recommended dose(s) for SAR444881 as monotherapy and in combination with pembrolizumab and/or cetuximab.

Both parts of study TCD17465 will enroll participants with tumor types known to express HLA-G [\[12-28, 31, 82, 177-179\]](#). In these tumor types the HLA-G-ILT2 inhibitory pathway may represent an important immune evasion mechanism employed by tumor cells to escape elimination by immune cells and so the clinical benefit potential of SAR444881 is believed to be higher. SAR444881 combinations escalation cohorts (Sub-Parts 1B/1C) will enroll participants with tumor types that pembrolizumab or cetuximab are either approved for their treatment or were demonstrated to have an acceptable safety profile in clinical trials [\[5, 158, 172, 174, 180-186\]](#). Sub-Part 1C SAR444881 in combination with cetuximab) will enroll participants with solid tumor types known to over-express EGFR [\[187\]](#).

The dose escalation part of the study will enroll multiple tumor types to assure an adequate participant accrual rate while the dose optimization/expansion part focuses on the following tumor types:

- **Gastric cancer:** HLA-G is an independent unfavorable prognostic factor reported to be expressed in 31% to 71% of patients
- **Lung cancer:** HLA-G is an independent unfavorable prognostic factor and its expression correlates to advanced disease stage. 34% to 75% of tumors were reported to be positive for HLA-G expression
- **Head and neck cancer:** HLA-G is an independent unfavorable prognostic factor reported to be expressed in 45% to 79% of patients
- **Colorectal cancer:** HLA-G is an independent unfavorable prognostic factor reported to be expressed in 64% to 72% of patients

Besides being known to express HLA-G [\[31, 127\]](#), the four dose optimization/expansion cancer types were selected based on their known responsiveness to immunotherapies such as checkpoint inhibitors. PD-1 immune checkpoint inhibitors have demonstrated a clinical benefit and an acceptable safety profile and are approved for the treatment of gastric adenocarcinoma, non-small cell lung cancer and squamous cell carcinoma of the head and neck [\[4, 175, 188-193\]](#).

ILT2 expression by tumor infiltrating lymphocytes was found to be upregulated following anti-PD-1 therapy [150]. In addition, T_{EMRA} CD8 cells, a subset of T lymphocytes known to express ILT2, are also upregulated following PD-1 blockade [109]. Finally, higher baseline soluble HLA-G levels were found to be associated with reduced response and shorter survival in NSCLC patients treated with an anti-PD1 [126] further demonstrating that the HLA-G-ILT2 pathway may represent a resistance mechanism to PD(L)-1 blockade therapy.

Most participants enrolled in the dose optimization/expansion phase of TCD17465 are expected to have failed PD(L)-1 checkpoint inhibitor therapy, allowing the study to evaluate the potential benefit of SAR444881 in an advanced cancer patient population which is becoming more prevalent.

As a first-in-human study, TCD17465 is designed to incorporate multiple safety measures to mitigate potential risk for participants and to allow early identification and appreciation of any potential safety issues. Measures include conservative pattern of dose escalation with standard intervals between doses, a staggered participant enrollment approach in the dose escalation cohorts, safety assessments in both study parts based on continuous reporting of adverse events during and after SAR444881 treatment and the measurement of vital signs, electrocardiograms, physical examinations, and clinical laboratory, and establishing a Safety Review Committee (SRC) chartered with monitoring participants' safety throughout the study. Bayesian toxicity monitoring on DLT (See Section 11.3.7) will also be conducted for continuous evaluation of toxicity events throughout enrollment for all optimization/expansion cohorts.

3.2.7 Rationale for Dose Selection

The objective of Part 1 of the study, during which SAR444881 will be administered in multiple ascending doses, is to assess the safety and tolerability of SAR444881.

SAR444881 Escalation Phase Starting Dose

The Minimal Anticipated Biological Effect Level (MABEL) approach along with available nonclinical safety pharmacology and toxicology data were used to define the SAR444881 starting dose for entry into human study. The starting dose selected for SAR444881 in Part 1 is 0.1 mg/kg, which corresponds to the MABEL dose obtained by pharmacological activity assessment *in vitro*. The dose of SAR444881 is planned to be escalated up to 20 mg/kg.

The MABEL of SAR444881 was determined based on the EC₂₀₋₅₀ observed in relevant *in vitro* models. Models included SAR444881 concentration-pharmacology effect curves from *in vitro* functional phagocytosis, NK cell cytotoxicity, and functional T cell activity assays. EC₂₀ and EC₅₀ ranged from [REDACTED] µg/mL to [REDACTED] µg/mL, respectively. Based on these experiments a SAR444881 concentration of [REDACTED] µg/mL should be considered in the low range of the minimal effective dose.

Additional *in vitro* studies included the evaluation of SAR444881's receptor occupancy (RO) in immune cells. RO assays evaluated monocytes, macrophages, NK cells and T_{EMRA} cells as isolated cells or in the context of total PBMC. SAR444881 concentrations of [REDACTED] µg/mL yielded a RO of [REDACTED] across the different immune cell types studied and the mean concentration yielding a RO of [REDACTED] was [REDACTED] µg/mL. A SAR444881 concentration of 1 µg/mL is expected to yield an ILT2 RO of [REDACTED] in immune cells relevant to its proposed mechanism of action. Finally, based on *in vivo* xenograft

mouse studies, a serum concentration of 1 µg/mL of SAR444881 is expected at a dose of approximately 0.1 mg/kg, which was determined as the MABEL for SAR444881.

Additional details on determining the MABEL of SAR444881 can be found in the Investigator's Brochure.

SAR444881 is an IgG4 antagonist antibody with no detected Fc-related effector functions. SAR444881 does not induce significant proliferation or secretion of pro-inflammatory cytokines from human PBMC and does not enhance phagocytosis of macrophages against not-target cells. In the pivotal Cynomolgus monkeys GLP toxicology study SAR444881 was well-tolerated at doses up to 100 mg/kg which was considered as the No Observed Adverse Effect Level (NOAEL).

Taken together, these results support 0.1 mg/kg as a safe starting dose for SAR444881 in this first-in-human study. Subsequent dose level increases in Part 1 are designed to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

In Sub-Parts 1B/1C (SAR444881 combinations dose escalation), SAR444881 will be administered in escalating doses in combination with pembrolizumab or with cetuximab. The starting dose of SAR444881 will be 1 mg/kg or one dose level below the established SAR444881 monotherapy MTD, the lower of the two. The two combination cohorts will start enrolling participants once a decision has been made to escalate SAR444881 to the 3 mg/kg dose level or once a SAR444881 MTD of lower than 3 mg/kg has been established in the SAR444881 single agent dose escalation (Sub-Part 1A). All available safety data from single agent escalation cohorts, e.g. occurrence of DLTs in lower doses, will be taken into consideration in the decision to start enrollment to combinations dose escalation cohorts and enrollment may start only after a SAR444881 dose higher than 1 mg/kg has been determined to be safe.

Opening combinations dose escalation cohorts at a lower SAR444881 dose than the established SAR444881 monotherapy recommended dose(s) addresses the potential risk of overlapping toxicities between SAR444881 and pembrolizumab or cetuximab, allows for a thorough assessment of potential effective SAR444881 doses when administered in combination and accelerates the development process while assuring participant safety.

SAR444881 Doses for Dose Optimization/Expansion

Clinical experience with SAR444881 is described in [Section 3.2.4](#). Overall, SAR444881 has proven safe and well tolerated as a single agent or in combination with either pembrolizumab or cetuximab at doses up to 20 mg/kg with no DLTs observed to date. In addition to this, preliminary clinical responses have been observed in several tumor types at the 3 mg/kg and 10 mg/kg dose levels, where SAR444881 was administered either as a single agent or in combination with either pembrolizumab or cetuximab.

SAR444881 is administered either on a Q2W schedule (Sub-Parts 1A and 1C) or a Q3W schedule (Sub-Part 1B) at dose levels ranging from 0.1-20 mg/kg. To date, SAR444881 dose levels tested on the Q2W schedule are 0.1 mg/kg (n=5 Part 1A participants), 0.3 mg/kg (n=3 Part 1A participants), 1 mg/kg (n=3 Part 1A participants and n=3 Part 1C participants), 3 mg/kg (n=7 Part 1A participants and n=6 Part 1C participants), 10 mg/kg (n=7 Part 1A participants and n=6 Part 1C participants), and

20 mg/kg (n=6 Part 1A participants and n=7 Part 1C participants). For the Q3W in Part 1B, SAR444881 dose levels that have been tested are 1 mg/kg (n=4 participants), 3 mg/kg (n=7 participants), 10 mg/kg (n=6 participants), and 20 mg/kg (n=6 participants). Thus far, the MAAD for all three sub-parts is ■ mg/kg; ■ mg/kg.

PK exposure of SAR444881 was nearly linear and dose proportional from ■ mg/kg to ■ mg/kg in both Q2W and Q3W regimens based on preliminary population pharmacokinetic (PopPK) modeling. The PopPK/PD modeling suggested that maintaining a median target receptor occupancy (RO) exceeding 90% was achievable at ■ mg/kg or higher in both Q2W and Q3W regimens. To ensure >90% target RO in the majority of participants ($\geq 90\%$ of the population), it is preferable for the 10th percentile of the simulated RO values to be greater than 90%. This requirement can be fulfilled with a dosage of ■ mg/kg or higher in the Q2W regimen or ■ mg/kg or higher in the Q3W regimen based on the preliminary PopPK/PD modeling.

Analysis of the ILT2 RO assay demonstrated sustained, nearly saturated levels of RO in peripheral monocytes at SAR444881 dose levels of ■ mg/kg and above. In addition, the analysis of exploratory ■ data indicated that SAR444881 induced an upregulation of ■ at the doses of ■ mg/kg or higher.

The process of how the totality of these data has been leveraged to define the doses for optimization (Part 2, Stage 1) is described in [Section 5.1.2.1](#). Briefly, all available relevant data will be leveraged for this purpose including, but not limited to, ■. The doses of SAR444881 have been decided by the Sponsor and approved by the Safety Review Committee prior to initiation of enrollment in combination optimization/monotherapy expansion phase (Part 2).

Safety data from Part 1 were to indicate that MAAD (■ mg/kg for all sub-parts) is safe. Further, the PK and PD data described above demonstrate that SAR444881 doses 3 mg/kg or higher at both Q2W and Q3W regimens are candidate doses for optimization. However, efficacy data to date demonstrate that clinical responses are only observed at the ■ mg/kg and ■ mg/kg dose levels. Accordingly, the ■ mg/kg dose level will be used in for dose optimization in Part 2, Stage 1. Per cohort SAR444881 doses for Part 2, Stage 1 are shown in [Table 3-1](#).

Table 3-1 – Per Cohort SAR444881 Dose Levels for Dose Optimization (Part 2, Stage 1)

Cohort	Study Sub-Part	Disease	SAR444881 Dose	Dosing Frequency
A1	2A	Non-squamous NSCLC	10 mg/kg	Q3W
B1	2A	GC/GEJ	10 mg/kg	Q3W
C1	2A	CRC any <i>RAS</i>	10 mg/kg	Q2W
D1	2B	Cholangiocarcinoma	10 mg/kg	Q2W
E1	2A	NSCLC	10 mg/kg	Q2W

3.2.8 **Anticipated Risks**

A Phase 1/2 FIH Study TCD17465 is currently ongoing in adult participants with advanced or metastatic solid tumors. This is an open-label, multicenter, dose escalation and expansion study designed to evaluate the safety and tolerability of SAR444881 administered as a single agent and in combination with pembrolizumab or with cetuximab. The study is ongoing and the safety profile of SAR444881 has not been characterized. Limited human safety data in adults is available and can be found in [Section 3.2.4](#).

3.2.8.1 **SAR444881**

SAR444881 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody, that binds to ILT2, an inhibitory receptor belonging to the LILRB family. ILT2 is expressed on a range of immune cells including macrophages, NK and T cells, and recognizes classical and non-classical MHC class I molecules, with a high affinity for HLA-G.

To the best of the Sponsor's knowledge there are no reports of previous experience in clinical trials with anti-ILT2 antibodies or other therapeutics targeting the HLA-G-ILT2 pathway. There is however substantial experience in cancer patients with approved and investigational products that prevent the suppression of macrophages, NK cells and CD8⁺ T-lymphocytes.

The nonclinical toxicological assessment of SAR444881 did not identify any apparent toxicities or safety risks (see [Section 3.2.2.2](#)). In the pivotal GLP repeat-dose toxicology study of SAR444881 in Cynomolgus monkeys SAR444881 was well tolerated with no obvious treatment related adverse effects, no gross or microscopic treatment related pathological findings, and no mortality observed. No treatment-related toxicities were observed at any dose level up to 100 mg/kg. In addition, *in vitro* studies in human blood have demonstrated that SAR444881 does not induce proliferation of PBMC or significant pro-inflammatory cytokine secretion. Finally, no off-target binding of SAR444881 was observed in human tissues cross-reactivity studies.

By enhancing the activity of immune cells, treatment with SAR444881 may result in inflammatory, autoimmune-like side effects. Such inflammatory adverse events, often termed immune-related adverse events (irAEs) or immune-mediated adverse events (imAEs), have been observed with other immune checkpoint blockade therapies.

Diverse imAEs have frequently been observed with immune checkpoint inhibitors such as anti-PD-1, anti-PD-L1 and anti-CTLA4 drugs, that enhance CD8⁺ T-lymphocyte function. The reported incidence of any-grade imAEs associated with single-agent immune checkpoint inhibitor treatment ranges widely across agents and trials, from approximately 15% to 90% [194]. Most imAEs are mild in intensity but around 10% of patients treated with anti-PD-1 checkpoint inhibitors will develop severe, sometimes life-threatening, Grade 3–4 imAEs [195, 196]. A 2015 meta-analysis examining data from 1,265 patients across 22 clinical trials of anti-CTLA-4 antibodies, reported an overall incidence of 72% for any grade imAEs and 24% for high-grade imAEs. In a meta-analysis of anti-PD-1/PD-L1 agents, any-grade and severe-grade imAEs occurred in 26.8% and 6.1% of patients, respectively [194]. Severe imAEs requiring immunosuppression and hold or discontinuation of treatment are estimated between 0.5% and 13% for immune checkpoint monotherapy.

Anti-CTLA-4 and anti-PD-1/PD-L1 reported studies have mainly drawn attention to colitis or pneumonitis because of their frequency and severity. However, nearly all organs can be affected by immune-mediated toxicities [195]. imAEs can affect the skin (maculopapular rash, vitiligo, psoriasis, Lyell syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome), the gastrointestinal tract (enterocolitis, gastritis, pancreatitis), the endocrine glands (hypo or hyperthyroidism, hypophysitis, adrenal insufficiency, diabetes), the lung (pneumonitis, pleural effusion, sarcoidosis), the nervous system (peripheral neuropathy, aseptic meningitis, Guillain–Barré syndrome, encephalitis, myelitis, myasthenia), the liver (hepatitis), the kidney (granulomatous interstitial nephritis, lupus-like glomerulonephritis), hematological cells (hemolytic anemia, thrombocytopenia, neutropenia), the musculo-articular system (arthritis, myopathies), the heart (pericarditis, cardiomyopathy) or the eyes (uveitis, conjunctivitis, blepharitis, retinitis).

Immune checkpoint inhibitor therapies that target CD8⁺ T-lymphocytes can usually continue in the presence of mild irAEs with close monitoring. However, moderate to severe imAEs may be associated with severe declines in organ function and quality of life, and fatal outcomes have been reported; hence, these toxicities require early detection and proper management [197]. Most of the anti-PD-1 imAEs, with the exception of the endocrine effects, resolve with immune-modulating medication, such as corticosteroids or TNF α blockade, and/or withholding the drug for brief periods [4, 175].

Drugs that enhance the anti-tumor activity of macrophages and NK cells are in human clinical trials. In early stage trials, Hu5F9-G4/magrolimab and ALX148, that block the macrophage inhibitory CD47-SIRP α pathway, were well tolerated and most toxicities were mild to moderate. No treatment-related autoimmune phenomena analogous to those reported with anti-PD-1/PD-L1 were observed and infusions were easily administered in an outpatient setting [198, 199]. In addition, in studies combining CD47-targeting drugs with the tumor targeting antibodies rituximab and trastuzumab and with the anti-PD-1 pembrolizumab, the combinations were reported to be well tolerated [167, 200, 201].

One recurrent adverse event reported for CD47-targeting drugs is anemia, which is an expected on-target, pharmacodynamic effect of blocking this antigen. CD47 blockade can accelerate the elimination of aging red blood cells and is related to the unmasking of phagocytic signals on these cells. As red blood cell elimination is not known to be dependent on expression of ILT2 ligands, such as HLA-G or classical HLA-I molecules, anemia is not an expected adverse event of SAR444881.

Investigational drug products targeting inhibitory NK cell receptors have also been studied in clinical trials. Lirilumab, a monoclonal antibody targeting the KIR receptor, was generally well tolerated in early stage oncology trials. Few transient, usually mild to moderate, infusion-related skin reactions and one possibly related Grade 2 allergy were the only immune related disorders observed [202, 203]. Lirilumab was also studied in combination with the anti-PD-1 nivolumab. No additional safety concerns were observed with the combination therapy compared to nivolumab monotherapy, with the exception of an increase in low-grade infusion-related reactions that were clinically manageable [204]. Monalizumab, a monoclonal antibody targeting the inhibitory NKG2A receptor, was also well tolerated as a single agent with no reported DLTs or serious AEs in an early stage clinical trial [205]. It was also studied in cancer patients in combination with cetuximab and the anti-PD-L1 durvalumab

[206-208]. The monalizumab combinations were well tolerated with no additional safety concerns compared to the three drugs alone.

Although experience with immune checkpoint inhibitors targeting macrophages, NK and T cells points to an acceptable safety profile, careful evaluation of immune-mediated autoimmune responses to SAR444881 is required. Immunomodulating drugs, such as SAR444881, can affect multiple organs with a wide range of potential adverse events. imAEs are most commonly seen in the skin; GI tract; lungs; liver and endocrine, thyroid, adrenal, pituitary, musculoskeletal, renal, nervous, hematologic, cardiovascular, and ocular systems. Any adverse events affecting these organs and systems occurring during treatment and in the first months after discontinuation of SAR444881 should be considered as potentially treatment-related.

HLA-G binds and activates the ILT2 receptor pathway. It is expressed at the fetal–maternal interface on the extravillous cytotrophoblast, placenta and amnion where it is thought to confer protection to the fetus from the maternal immune system. The expression of ILT2 in activated decidual CD4⁺ T cells may also be important for successful pregnancies. Considering its potential role in fetal–maternal tolerance, blocking the HLA-G-ILT2 pathway with SAR444881 may impair the normal pregnancy process. To minimize this risk, women of childbearing potential enrolling to the proposed first-in-human study must have a negative serum or urine pregnancy test and must agree to follow instructions for method(s) of contraception. Males enrolling to the study, who are sexually active with women of childbearing potential (WOCBP), must agree to follow instructions for method(s) of contraception as well.

The HLA-G protein was also found to be expressed in healthy adult corneas where it may contribute to the maintenance of the immune-privileged status of the tissue [84]. Uveitis is a recognized immune-mediated adverse event of immune checkpoint inhibitors however occurs less frequently than other immune-mediated adverse events. In a recent study the reported prevalence of moderate-to-severe ocular complications associated with anti-PD-(L)1 was 0.4% [209]. In the pivotal GLP toxicology study of SAR444881 in Cynomolgus monkeys no treatment-related abnormal ophthalmic findings were observed in clinical and histopathology examinations.

Based on the ophthalmic assessment in the GLP toxicology study and the reported incidence of immune-mediated ocular adverse events, the risk of corneal or other ocular toxicity in patients treated with SAR444881 is considered to be low. However, ocular symptoms, such as pain, blurred vision, tearing, or sensitivity to light, and ocular signs should be given careful attention.

Drug-related infusion reactions are commonly reported for monoclonal antibody drugs and have been reported for immune checkpoint inhibitors. As with the administration of any immunoglobulin, infusion-related reactions (IRRs) and acute immunoglobulin E (IgE)–mediated allergic reactions may occur and may be severe and result in death. If such a reaction were to occur with SAR444881 infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, dizziness or lightheadedness, myalgia, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Acute infusion reactions can manifest within 24 hours from the first administration of the monoclonal antibody, but they appear most frequently from 10 minutes to 4 hours after beginning the administration [210]. Although based on preclinical data there is only minimal potential for cytokine release (refer to Section 3.2.2.2), it cannot be excluded at this stage, that CRS may occur as

IRR or late-onset IRR^[00]. Participants should be carefully monitored for infusion reactions during SAR444881 administration. If an acute infusion reaction or CRS is noted, participants should be managed according to [Section 9.4](#).

SAR444881 is only to be administered in a hospital or clinical environment under the close supervision of an experienced clinician. Detailed instructions on dosage, infusion rate, and administration of SAR444881 are provided in [Section 7.4](#).

An urgent need exists for new treatments for cancer patients with advanced disease that has progressed or not responded to systemic therapies. As SAR444881 is an investigational agent, it is possible that unforeseen, unknown, or unanticipated adverse reactions may occur. However, based on the nonclinical safety profile of SAR444881 and the clinical safety profile of cancer drugs with a similar mechanism of action, the potential safety risks should be considered acceptable. Based on all available information, the Sponsor concluded that there is an acceptable benefit-risk balance for the clinical investigation of SAR444881 in patients with unresectable or metastatic solid tumors who have progressed on standard of care treatment or are intolerant to standard treatment.

The current study, which aims to characterize the safety and tolerability of SAR444881, was designed to incorporate multiple safety measures to mitigate potential risk for patients and to allow early identification of any potential safety issues.

For the most up-to-date safety information for SAR444881, please refer to the SAR444881 IB.

3.2.8.2 Pembrolizumab

The safety profile of pembrolizumab is well characterized [\[5\]](#). Pembrolizumab is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. See [Appendix 6](#) for recommended management algorithms of immune-mediated AEs.

Important immune-mediated adverse reactions include the following:

- Immune-Mediated Pneumonitis: Pembrolizumab can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving pembrolizumab, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of pembrolizumab in 1.3% (36) of patients and withholding of pembrolizumab in 0.9% (26) of patients.

- Immune-Mediated Colitis: Pembrolizumab can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of pembrolizumab in 0.5% (15) of patients and withholding of pembrolizumab in 0.5% (13) of patients.
- Hepatotoxicity and Immune-Mediated Hepatitis: 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% (6) of patients and withholding of pembrolizumab in 0.3% (9) of patients.
- Immune-Mediated Endocrinopathies:
 - Adrenal Insufficiency: Pembrolizumab can cause primary or secondary adrenal insufficiency. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.
 - Hypophysitis: Pembrolizumab can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Hypophysitis occurred in 0.6% (17/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 94% (16/17) of patients with hypophysitis; of these, the majority remained on systemic corticosteroids.
 - Thyroid Disorders: Pembrolizumab can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Thyroiditis occurred in 0.6% (16/2799) of patients receiving pembrolizumab, including Grade 2 (0.3%). Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving pembrolizumab, including Grade 3 (0.1%) and Grade 2 (0.8%). Hypothyroidism occurred in 8% (237/2799) of patients receiving pembrolizumab, including Grade 3 (0.1%) and Grade 2 (6.2%). The majority of patients with hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with SCCHN, occurring in 16% of patients receiving pembrolizumab as a single agent or in combination with chemotherapy, including Grade 3 (0.3%) hypothyroidism.
 - Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis: Type 1

diabetes mellitus occurred in 0.2% (6/2799) of patients receiving pembrolizumab. All patients with Type 1 diabetes mellitus required long-term insulin therapy.

- **Immune-Mediated Nephritis with Renal Dysfunction:** Pembrolizumab can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 89% (8/9) of patients with nephritis. Nephritis led to permanent discontinuation of pembrolizumab in 0.1% (3) of patients and withholding of pembrolizumab in 0.1% (3) of patients.
- **Immune-Mediated Dermatologic Adverse Reactions:** Pembrolizumab can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson syndrome, DRESS syndrome, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving pembrolizumab, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 40% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of pembrolizumab in 0.1% (2) of patients and withholding of pembrolizumab in 0.6% (16) of patients.
- **Other Immune-Mediated Adverse Reactions:** The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received pembrolizumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
 - Cardiac/Vascular: Myocarditis, pericarditis, vasculitis
 - Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
 - Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur.
 - Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis
 - Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica
 - Endocrine: Hypoparathyroidism
 - Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection
- **Infusion-Related Reactions:** Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving pembrolizumab. If an acute infusion reaction is noted,

participants should be managed according to [Section 9.4](#).

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus.

Please refer to the country-approved product labeling (e.g., USPI, SmPC) for pembrolizumab for more detailed information.

3.2.8.3 Cetuximab

The safety profile of cetuximab is well characterized [\[158, 159\]](#).

Cetuximab can cause serious and fatal infusion reactions. Infusion reactions of any grade occurred in 8.4% of 1373 patients who received cetuximab across clinical trials. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion. The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose- α -1,3-galactose (alpha-gal). Consider testing patients for alpha-gal IgE antibodies using FDA-cleared methods prior to initiating cetuximab. Negative results for alpha-gal antibodies do not rule out the risk of severe infusion reactions. If an acute infusion reaction is noted, participants should be managed according to [Section 9.4](#).

Cetuximab can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 SCCHN patients treated with radiation therapy and cetuximab. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. Fatal cardiac disorders and/or sudden death occurred in 3% of 219 SCCHN patients treated with cetuximab in combination with platinum-based therapy and fluorouracil. In some studies, association of cardiovascular disorders with age ≥ 65 years or performance status has been observed.

Cetuximab can cause interstitial lung disease. Interstitial lung disease, including 1 fatality, occurred in $<0.5\%$ of 1570 patients receiving cetuximab in clinical trials. Confounding or contributing factors, such as concomitant chemotherapy known to be associated with interstitial lung disease, and pre-existing pulmonary diseases were frequent in fatal cases.

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of the 1373 patients who received cetuximab across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping cetuximab in most patients. Life-threatening and fatal bullous mucocutaneous

disease with blisters, erosions, and skin sloughing, has been observed in patients who received cetuximab. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis).

Cetuximab can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 colorectal cancer or head and neck cancer patients receiving cetuximab, including Grades 3 and 4 in 6% to 17%. When cetuximab was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No patient experienced Grade 3 or 4 hypomagnesemia. Hypocalcemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcemia may be increased. Hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating cetuximab.

Based on animal data and its mechanism of action, cetuximab can cause fetal harm when administered to a pregnant woman. There are no available data for cetuximab exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryo lethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development.

Please refer to the country-approved product labeling (e.g., USPI, SmPC) for cetuximab for more detailed information.

3.2.8.4 SAR444881 in Combination with Pembrolizumab or with Cetuximab

To the best of the Sponsor's knowledge no clinical data has been published on the combination of ILT2 blockade with other therapeutics.

Drugs that target macrophage and NK cell checkpoint inhibitors have entered clinical studies and have been studied in combination with PD-1 blockers and tumor targeting antibodies, including with cetuximab.

Magrolimab, an anti-CD47 blocking antibody, was studied in combination with cetuximab in a Phase 1b study in advanced solid tumor patients and in a Phase 2 study in colorectal cancer patients who have progressed on prior chemotherapy [168]. The combination had an acceptable safety profile, and no maximum tolerated dose was reached. Reported AEs were expected from cetuximab and magrolimab therapy. Treatment-related AEs (TRAEs) of any grade included dermatitis acneiform 36%, dry skin 33%, fatigue 32%, infusion reactions 31%, headache 30%, diarrhea 23%, nausea 23%, chills 23%, and anemia 22%. 1 of 46 patients in the Phase 2 study discontinued therapy due to a treatment related AE (Grade 2 infusion reactions/maculopapular rash). The anti-CD47 antibody was also studied in combination with an anti-CD20 antibody (rituximab) in patients with relapsed or refractory non-Hodgkin's lymphoma [167]. The safety profile of magrolimab plus rituximab showed no unacceptable side effects and no clinically significant safety events were observed. Dose-limiting side effects were rare, and an MTD was not reached. Most adverse events during treatment were of

Grade 1 and 2. The most common TRAEs were chills (41%), headache (41%), anemia (41%), and infusion-related reactions (36%). Most of the treatment related adverse events occurred within the first few weeks, and no long-term toxic effects were observed. Magrolimab was studied in combination with avelumab, an anti-PD-L1 antibody that has an active Fc-domain that can enhance tumor cell phagocytosis, in a Phase 1 study in solid tumor and ovarian cancer patients [211]. The combination had a tolerable safety profile, and no MTD was reached. Observed AEs were those expected from avelumab and magrolimab monotherapy experience. No Grade 4 or 5 treatment-related AEs occurred. TRAEs of any grade in more than 20% of patients included headache (62%), fatigue (47%), infusion related reaction (44%), pyrexia (38%), chills (35%), nausea (35%), anemia (24%), and vomiting (21%).

ALX148, a CD47 blocker, was studied in a Phase 1 trial in combination with established anticancer antibodies [157, 200, 201]. ALX148 in combination with an anti-HER2 (trastuzumab) or anti-PD-1 (pembrolizumab) was well tolerated and most TRAEs were of low grade and frequency. The most common treatment-related AEs in the combination with trastuzumab was fatigue (26.7%), and with pembrolizumab an increase in AST (15.4%). Treatment-related AEs of Grade 3 and above were of low frequency and only one DLT (autoimmune hemolytic anemia) was observed. One treatment related serious adverse event of febrile neutropenia in the trastuzumab combination was reported. Three treatment related serious adverse events in the pembrolizumab combination (1 autoimmune hemolytic anemia, 1 febrile neutropenia, and 1 neutropenia) were reported. There were no DLTs or treatment-related AEs of Grade 3 and above reported in patients treated with ALX148 in combination with pembrolizumab and chemotherapy and with ALX148 in combination with trastuzumab and chemotherapy.

The safety profiles of drugs enhancing the activity of NK cells have also been evaluated in clinical studies. Inhibitory Killer Immunoglobulin-like receptors (KIRs) negatively regulate the killing, by NK cells, of tumors expressing their HLA class I ligands. Lirilumab, an anti-KIR antibody, has been studied in a Phase 1 trial in patients with various hematologic or solid malignancies [202, 203]. Lirilumab was studied in combination with an anti-PD-1 checkpoint inhibitor in a Phase 1 study in patients with advanced solid tumors. No DLTs were reported with lirilumab in combination with nivolumab treatment and an MTD was not reached. TRAEs were generally Grade 1 or 2, and the most common TRAEs ($\geq 10\%$) among all treated patients were fatigue (20.8%), pruritus (18.9%), infusion-related reaction (17.6%), and rash (16.4%). Infusion-related reactions were Grade 1 or 2 and primarily occurred after the first infusion; pretreatment was not needed. TRAEs leading to discontinuation were reported in 12 patients (7.5%), with only treatment related pneumonitis (n = 3; all Grade 2) and diarrhea (n = 2; all Grade 2) occurring in more than 1 patient. No treatment-related deaths were reported. Investigators concluded that no additional safety concerns were observed with the lirilumab plus nivolumab combination therapy compared to nivolumab monotherapy, with the exception of an increase in low-grade infusion-related reactions that were clinically manageable [204]. Monalizumab, an anti-NKG2A blocking antibody, was studied in a Phase 1b trial in combination with cetuximab in SCCHN patients [206]. The combination of monalizumab and cetuximab was well tolerated with no additional safety concerns compared to the two drugs alone. All monalizumab-related AEs were Grade 1 or 2 except one Grade 3 fatigue. The most common TRAEs were asthenia/fatigue (24%) and headache (18%). No significant elevation of

proinflammatory cytokines following administration of monalizumab were observed. There were no DLTs reported with monalizumab plus cetuximab and an MTD was not reached. A Phase 2 study in advanced squamous cell carcinoma of the head and neck also found the combination of monalizumab and cetuximab to be well tolerated without potentiation of cetuximab side effects [207]. Monalizumab was also studied in a Phase 1 trial in combination with durvalumab, an anti-PD-L1 checkpoint inhibitor, in patients with advanced solid tumors [208]. The combination had a manageable toxicity profile with a safety profile similar to monotherapy profiles. No DLTs were observed in the dose escalation phase and an MTD was not reached. The most common treatment-related AEs were arthralgia, AST increased, hypothyroidism, pruritus, and rash. No fatal AEs or AEs leading to treatment discontinuation were reported.

Combinations of PD-1 and PD-L1 inhibitors with other T cell checkpoint inhibitory molecules, such as inhibitors of LAG3, T-cell immunoglobulin and mucin domain containing molecule 3 (TIM-3), V domain containing Ig suppressor of T-cell activation, and TIGIT, are also actively being pursued. Ipilimumab is a monoclonal antibody that binds to CTLA-4, a negative regulator of T-cell activity, and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. The combination of nivolumab and ipilimumab has demonstrated improved efficacy and has been approved for the treatment of several solid tumor types including melanoma, renal cell carcinoma, non-small cell lung cancer, pleural mesothelioma, colorectal cancer and hepatocellular carcinoma [155]. Although combination regimens offer the potential for enhanced efficacy, in general, observed toxicity with immune checkpoint inhibitor-based combination regimens is greater than that for checkpoint inhibitor monotherapy. Combined PD-1 plus CTLA-4 blockade triggers substantially more imAEs than anti-PD-1 agents alone, with high-grade events reported for 55% to 60% of individuals receiving combination therapy versus 10% to 20% of individuals receiving anti-PD-1 monotherapy. In the Phase 3 CheckMate 067 trial of nivolumab plus ipilimumab versus ipilimumab or nivolumab monotherapy, TRAEs occurred in 96% of patients receiving combination therapy and 86% of those treated with monotherapy. Although no unique toxicities were identified in patients receiving immune checkpoint inhibitor combination therapy, the incidence of high-grade imAEs for combination therapy (59%) was more than twice the incidence for single agent nivolumab (21%) and ipilimumab (28%). The percentages of patients discontinuing treatment due to any-grade TRAEs were 39%, 12%, and 16% for patients receiving combination therapy, nivolumab, and ipilimumab, respectively [194]. In a meta-analysis of combination studies in solid tumors, although the incidence of any TRAEs was similar between nivolumab plus ipilimumab and ipilimumab alone, ipilimumab monotherapy resulted in less serious AEs (Grade 3 or higher) than nivolumab plus ipilimumab. When comparing nivolumab plus ipilimumab to nivolumab alone the incidence of any TRAEs and serious TRAEs were elevated in nivolumab monotherapy than in the nivolumab plus ipilimumab combination however results varied across different dosages of nivolumab and ipilimumab in the combination group [212]. The most common reported adverse reactions (incidence $\geq 20\%$) of nivolumab in combination with ipilimumab are fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, decreased weight, and dizziness [155].

3.2.8.5 SAR444881 in Combination with Pembrolizumab and chemotherapy

Safety data from KEYNOTE-189 (pembrolizumab + pemetrexed and platinum) [213], from patients with non-squamous NSCLC, 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 median follow-up [214]. 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 safety profiles of carboplatin and pemetrexed are well characterized [215, 216]. The combination of SAR444881, pembrolizumab and chemotherapy (carboplatin, pemetrexed) are expected to have overlapping toxicities based on each drug's individual toxicity profile. Please refer to the latest version of the carboplatin and pemetrexed local labels for the most up to date safety data. A summary is included below.

Carboplatin: The primary adverse effects include the following: bone marrow suppression (anemia, neutropenia, thrombocytopenia), nausea and vomiting, hepatic function abnormalities, hypersensitivity /anaphylactoid reactions, peripheral neuropathy, ototoxicity and nephrotoxicity when administered with aminoglycosides and vision loss.

Pemetrexed: The primary adverse effects include the following: bone marrow suppression (anemia, neutropenia, thrombocytopenia), cutaneous reactions (serious and occasionally fatal bullous, blistering and exfoliative rashes) , nausea and vomiting, anorexia, hypersensitivity reactions, nephrotoxicity, interstitial pneumonitis and radiation recall.

3.2.8.6 Benefit/Risk Assessment

An urgent need exists for new treatments for cancer patients with advanced disease that has progressed or not responded to systemic therapies. As SAR444881 is an investigational agent, it is possible that unforeseen, unknown, or unanticipated adverse reactions may occur. In addition, as with any combination treatment, there is potential for overlapping toxicities between SAR444881 and pembrolizumab, cetuximab and chemotherapy regimens (carboplatin, pemetrexed). However, based on the nonclinical safety data of SAR444881 (Section 3.2.2.2), as a single agent and in combination, and the clinical safety profile of approved and investigational innate and adaptive immune checkpoint inhibitors (Sections 3.2.8.1 and 3.2.8.4), the potential safety risks should be considered acceptable. Pembrolizumab and cetuximab have demonstrated a manageable safety profile in participants with advanced solid tumors, including when administered in combination with additional therapeutics, and clinical experience with checkpoint inhibitors combinations indicate the potential for improvement in therapeutic response compared with single agent regimens (Section 3.2.3). The current study, which aims to characterize the safety and tolerability of SAR444881, was designed to incorporate multiple safety measures to mitigate potential risk for patients and to allow early identification of any potential safety issues. To mitigate risk from immune-mediated AEs, participant management algorithms for SAR444881-related AEs, based on prior experience with checkpoint inhibitors, have been included

([Appendix 6](#)).

Based on all available information, the Sponsor concluded that there is an acceptable benefit-risk balance for the clinical investigation of SAR444881 when administered alone and in combination with pembrolizumab or with cetuximab or with pembrolizumab and chemotherapy regimens (carboplatin, pemetrexed) in cancer patients with unresectable or metastatic disease who are refractory to or are not candidates for standard approved therapy.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints: Escalation (Sub-Parts 1A/1B/1C)

Objectives	Endpoints
Primary 1. To assess the safety and tolerability of SAR444881 when administered alone and in combination with pembrolizumab or with cetuximab 2. To determine the MTD or MAAD and the recommended dose(s) of SAR444881 for optimization/expansion when administered alone and in combination with pembrolizumab or with cetuximab	1. Incidence of Serious Adverse Events (SAEs), incidence and severity of treatment-emergent AEs (TEAEs) coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the CTCAE v5.0, laboratory abnormalities classified by severity using CTCAE v5.0 2. Incidence of TEAEs meeting protocol defined DLT criteria
Secondary (all apply to SAR444881 monotherapy and SAR444881 in combination with pembrolizumab or with cetuximab) 1. To assess preliminary anti-tumor activity of SAR444881 2. To characterize the PK of SAR444881 3. To characterize the immunogenicity of SAR444881	1. Objective Response Rate (ORR) defined as the proportion of participants with a best overall response of complete response (CR) or partial response (PR) per RECIST v1.1 2. PK parameters of SAR444881 (C_{max} , C_{trough} , T_{max} , $T_{1/2}$, AUC) 3. Incidence of anti-drug antibodies (ADA), SAR444881
Exploratory 1. [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

Table 4-2: Objectives and Endpoints: Optimization/Expansion (Part 2)

Objectives	Endpoints
Primary 1. To assess preliminary anti-tumor activity of SAR444881 2. To define the optimal dose of SAR444881 in combination with pembrolizumab, with cetuximab, or with pembrolizumab and chemotherapy (Sub-Part 2A only)	1. ORR per RECIST v1.1 (other datapoints may be utilized to supplement assessment of optimal SAR444881 dose)
Secondary 1. To assess additional parameters of anti-tumor activity of SAR444881 2. To further assess the safety and tolerability of SAR444881 3. To further characterize the PK of SAR444881 4. To further characterize the immunogenicity of SAR444881	1. PFS defined as the time from the date of first dose of study drug to the date of first documented disease progression or death due to any cause, whichever occurs first, to estimate median PFS using Kaplan-Meier (K-M) methodology; PFS rate at 3, 6, 9, 12 months, and up to 24 months per RECIST v1.1; DCR; Duration of Response (DoR) defined as the duration between first documentation of CR or PR to first documentation of disease progression or death from any cause, whichever occurs first 2. Incidence of SAEs and TEAEs, as described above 3. PK parameters of SAR444881 (C_{max} , C_{trough} , T_{max} , $T_{1/2}$, AUC) 4. Incidence of ADA, including nADA, to SAR444881

Exploratory

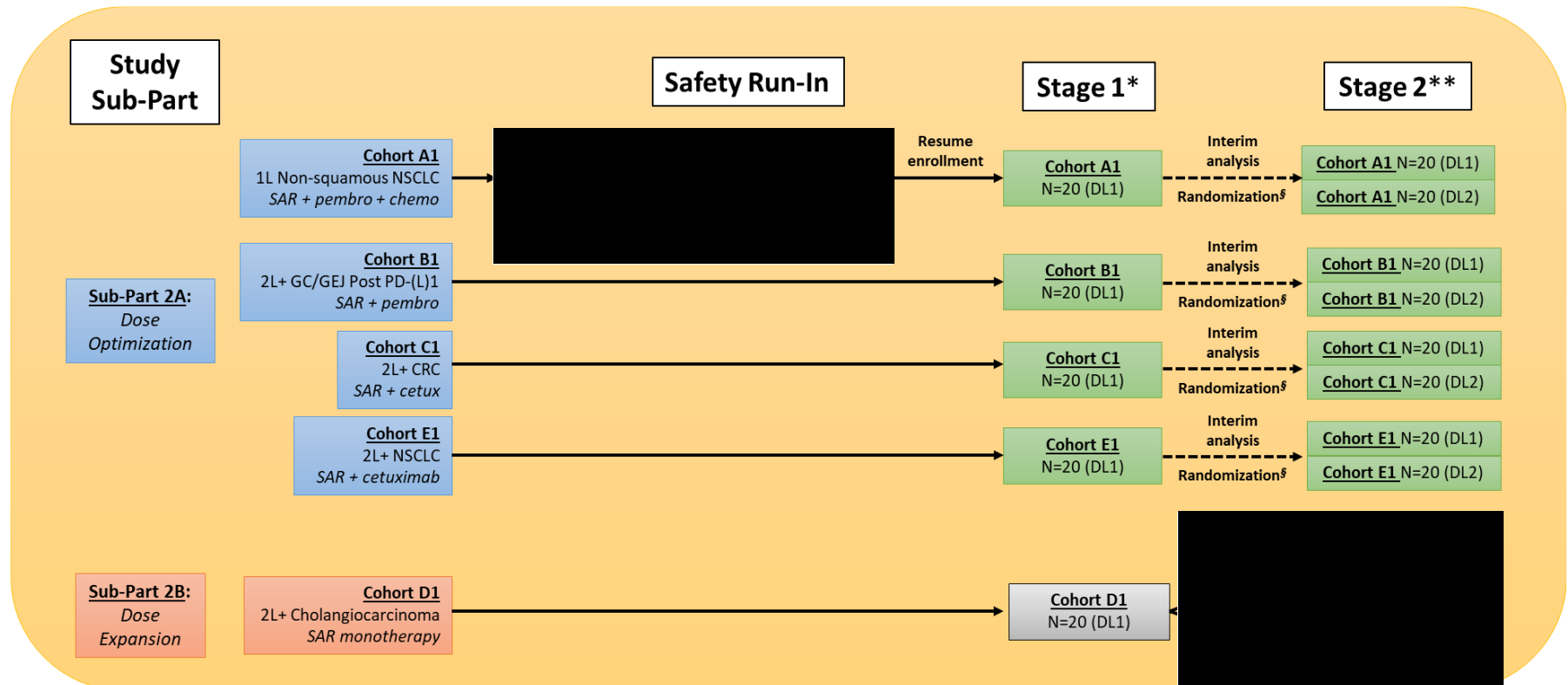
5 STUDY DESIGN

5.1 Overall Design

This is an open-label, multicenter, Phase 1/2, first-in-human study of intravenous SAR444881, a humanized monoclonal IgG4 antibody, targeting the Ig-like transcript 2 (ILT2) immune inhibitory receptor. The study will evaluate SAR444881 as a single agent and when combined with pembrolizumab or with cetuximab and/or chemotherapy and will enroll cancer patients with advanced solid tumors where no other standard of care treatment option is available. Given the known mechanism of action of ILT2 and its potential role in cancer, the study focuses on tumor types known to express HLA-G. Tumor types included in SAR444881-cetuximab combination cohorts are tumors known to over-express the EGFR protein.

The proposed study will be comprised of two parts – a dose escalation phase (Part 1) and a dose optimization/expansion phase (Part 2). Part 1 is comprised of three sub-parts: SAR444881 administered alone (Sub-Part 1A), SAR444881 administered in combination with pembrolizumab (Sub-Part 1B), and SAR444881 administered in combination with cetuximab (Sub-Part 1C). Part 2 is composed of two sub-parts: a dose optimization part where up to two doses of SAR444881 per indication are administered in combination with pembrolizumab, cetuximab, and/or chemotherapy (Sub-Part 2A); and a dose expansion part where SAR444881 is administered alone (Sub-Part 2B). The study design schematic is presented in [Figure 1](#) and [Figure 5.2](#).

Figure 5.2: Overall design for dose optimization/expansion



Two stage design to facilitate dose optimization: *Stage 1 – preliminary assessment of efficacy at a single dose level (DL1; n=20); **Stage 2 – if efficacy in Stage 1 is deemed acceptable, additional participants will be enrolled and randomized to one of two dose levels: DL1 (n=20) and DL2 (n=20) (note, it is anticipated that DL1 will be higher than DL2); see text for further details. §Initiation of Stage 2, with randomization to one of two SAR444881 dose levels will only occur if acceptable efficacy is observed in Stage 1.

1L = first line; 2L+ = second line or later; NSCLC = non-small cell lung cancer; GC/GEJ = gastric cancer or gastro-esophageal junction adenocarcinoma; CRC = colorectal carcinoma; cetux: cetuximab; chemo: chemotherapy (carboplatin/pemetrexed); pembro: pembrolizumab; SRC: Study Review Committee; SAR: SAR444881; DL: dose level.

The objectives for the dose escalation phase (Part 1) are to assess the safety and tolerability, and to determine the MTD (or MAAD, if no MTD is reached) and the recommended dose(s) of SAR444881 when administered alone and in combination with pembrolizumab or with cetuximab. Dose escalation in all three sub-parts will follow a standard “3 + 3” design enrolling at least 3 participants per dose level cohort. The dose escalation phase of the study will enroll cancer patients with advanced disease who are refractory to or are not candidates for standard approved therapy.

Part 2, which includes five cohorts, is designed to assess preliminary anti-tumor activity and optimal dose of SAR444881 as a single agent and in combination in cancer patients with select advanced solid tumors known to express HLA-G and a likelihood of sensitivity to immunotherapies as observed with other checkpoint inhibitors. It will enroll participants with unresectable or metastatic disease. The proposed study aims to establish proof-of-concept that combining SAR444881 as a monotherapy or in combination with one or more of the following: 1) the anti-PD1 monoclonal antibody pembrolizumab; 2) the anti-EGFR monoclonal antibody cetuximab; or 3) pembrolizumab and chemotherapy. Part 2 is divided into two sub-parts: in Sub-Part 2A (Dose Optimization), the preliminary anti-tumor activity and optimal dose of SAR444881 is assessed in combination with the aforementioned anti-tumor agents; and in Sub-Part 2B (Dose Expansion), the preliminary anti-tumor activity of SAR444881 is assessed as a monotherapy. The indications under investigation are described in [Table 5.1-1](#). However, it is to be noted that additions of new cohorts in other indications may be added at a later stage of development.

Table 5.1-1 – Overview of study cohorts

Cohort	Study Sub-Part	Study Intervention	Disease
A1	2A	SAR444881 + pembrolizumab + carboplatin + pemetrexed as 1L therapy	Non-Squamous NSCLC
B1	2A	SAR444881 + pembrolizumab as 2L and later therapy	GC/GEJ
C1	2A	SAR444881 + cetuximab as a 2L and later therapy	CRC any <i>RAS</i>
D1	2B	SAR444881 as a 2L and later therapy	Cholangiocarcinoma
E1	2A	SAR444881 + cetuximab as 2L and later therapy	NSCLC

1L = first line; 2/3L = second or third line; 3L = third line; NSCLC = non-small cell lung cancer; GC/GEJ = gastric cancer or gastro-esophageal junction adenocarcinoma; CRC = colorectal carcinoma; PD-L1 = programmed cell death-ligand 1; TBD = to be determined.

In Sub-Part 2A, a two-stage design will be implemented to conduct dose optimization

for each indication with combination therapy:

- Stage 1 (Preliminary Assessment): Enroll 20 patients and treat the patients at one potential recommended dose identified from dose escalation in each indication to assess preliminary efficacy, safety, PK, and PD data.
- Stage 2 (Randomization): Randomize 40 patients 1:1 into the two recommended doses with each indication that showed activity in Stage 1 to support selection of optimal dose for the indication. [REDACTED]

More details of two-stage design are detailed in [Appendix 9](#).

In Stage 1 of Sub-Part 2B, the efficacy of SAR444881 monotherapy will be evaluated at 20 patients in cholangiocarcinoma. The indication for Cohort D1 was chosen based on emerging data from the dose-escalation phase, combination optimization cohorts, landscape, and internal preclinical work. [REDACTED]

Participants in the study will complete up to three periods in the study: **Screening** (within 28 days prior to start of the study drug), **Treatment** (28 days/cycle [Part 1A, 1C, Part 2A Cohort C1 and E1, and Part 2B Cohort D1] or 21 days/cycle [Part 1B and Part 2A Cohorts A1 and B1]; participants will be treated until meeting criteria for discontinuation), and **Safety Follow-Up** (approximately 30, 60, and 90 days from study drug(s) discontinuation).

A schematic for study periods and participant flow is presented in [Figure 5.3](#) for Cohorts C1, D1, and E1 and [Figure 5.4](#) for Cohorts A1 and B1.

Figure 5.3: Schematic for study periods and participant flow for Part 2 Cohorts C1, D1, and E1

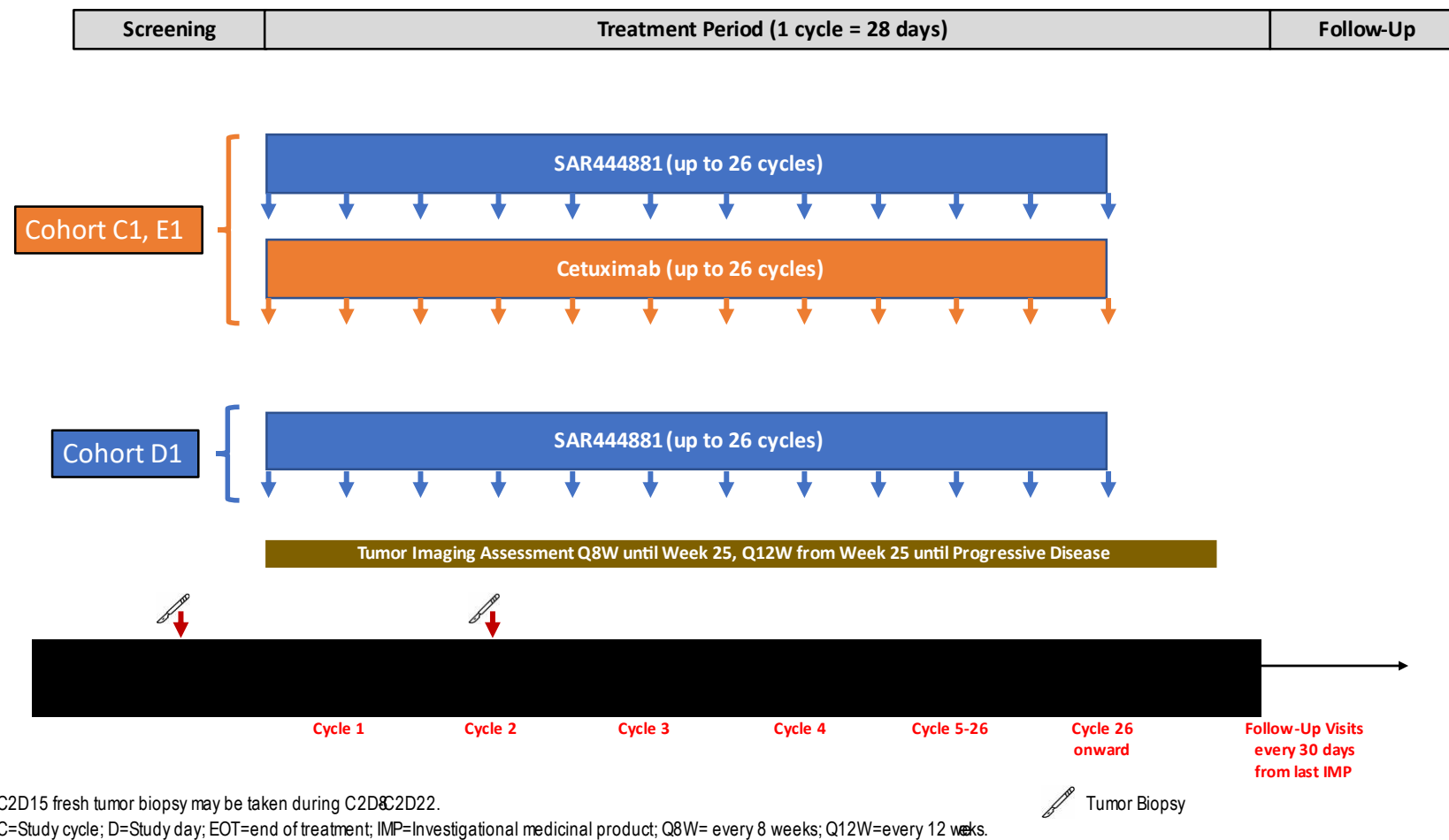
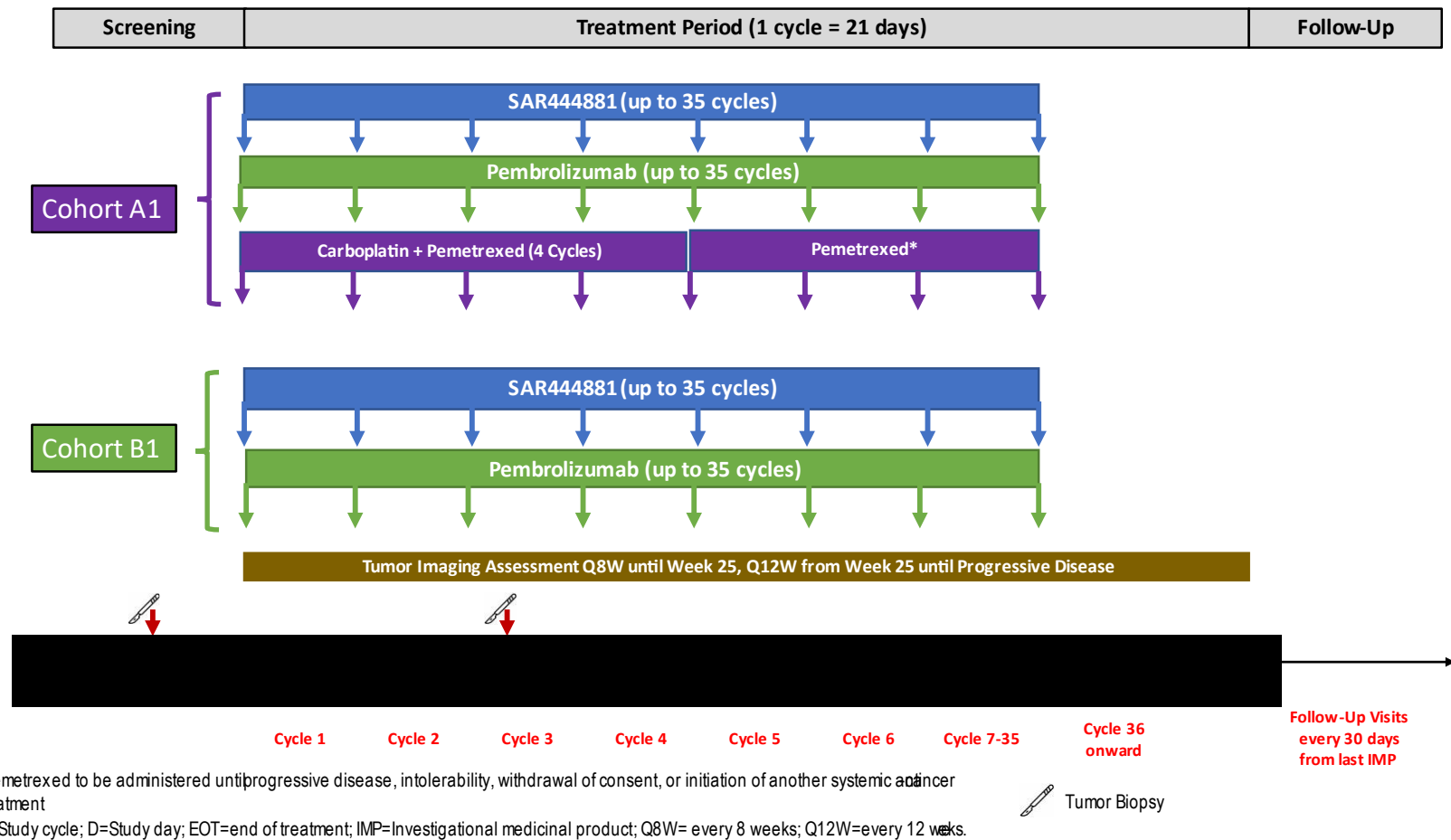


Figure 5.4: Schematic for study periods and participant flow for Part 2 Cohorts A1 and B1



5.1.1 Screening Period

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). The screening assessments are shown in [Table 2-1](#). If a participant exceeds the screening period due to a study-related procedure (e.g., scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be re-consented, but does not require a new Subject Number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility.

5.1.1.1 Medical History and Demographic Data

The participant's general demographics (e.g., date of birth, sex, ethnicity, and race) along with relevant medical history will be collected. Medical history includes clinically significant diseases (all active conditions and any condition diagnosed within the prior 5 years that are considered to be clinically significant), all surgeries, cancer history (including all prior cancer therapies [including adjuvant and neoadjuvant therapies] and procedures), reproductive status, any toxicity or allergy related to previous treatments, and smoking, alcohol, and drug abuse history.

5.1.1.2 Definition of Baseline Assessments/Values

Baseline is considered the last available and valid assessment performed or value measured within 28 days before the first administration of study treatment, unless otherwise stated. Baseline could be the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, Vital Sign).

5.1.2 Treatment Period

All participants will be treated until meeting criteria for treatment discontinuation ([Section 8](#)). Participants will be permitted to continue treatment beyond initial RECIST v1.1 defined Progressive Disease (PD) if they meet specific criteria defined in the study protocol. See [Section 5.1.4](#) for further details. The treatment period in all study cohorts will consist of 4-week treatment cycles except Sub-Part 1B in which a treatment cycle will be 3 weeks in length. Tumor assessments will occur every 8 weeks for the first 24 weeks and then every 12 weeks. Continuous safety evaluation and scheduled tumor assessments will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

Study visits in Part 1 will be performed weekly for the first 2 cycles following the first dose of study treatment(s). Study visits at Cycle 3 and beyond will be every 2 weeks in Sub-Parts 1A/1C. In Sub-Part 1B, visits will be performed on C3D1 and C3D8 and on day one of each treatment cycle thereafter, i.e., every 3 weeks. An additional study visit is required in the dose escalation phase in Cycle 1 Day 2 for safety assessments and to collect samples for PK and biomarker testing (see [Sections 10.6](#) and [10.7](#) for further details). In Part 2 (Dose Optimization/Expansion), study visits will be performed every week for Cycle 1 and Cycle 2. Study visits at Cycle 3 and beyond will be every 2 weeks.

The frequency and mode of administration of SAR444881 will be the same in both study parts, except Sub-Part 1B (pembrolizumab combination escalation). SAR444881 will be administered

intravenously, every 2 weeks (Q2W) in Sub-Parts 1A/1C and Sub-Part 2A/B Cohorts C1, D1, and E1. In Sub-Part 1B and Sub-Part 2A Cohorts A1 and B1, SAR444881 will be administered intravenously, every 3 weeks (Q3W). SAR444881 will be infused over [REDACTED] minutes at all dosage levels except for the 0.1 mg/kg dosage which will be infused over [REDACTED] minutes. The dosage and mode of administration of pembrolizumab, cetuximab, pemetrexed, and carboplatin will be according to the drugs' Prescribing Information. Pembrolizumab will be administered intravenously at a dose of 200 mg, over [REDACTED] minutes, Q3W. Cetuximab will be administered intravenously at a dose of 500 mg/m², over [REDACTED] minutes, Q2W. Participants treated with cetuximab will be premedicated with a [REDACTED] [REDACTED] intravenously. For further details see [Section 7](#).

In SAR444881 combination cohorts, [REDACTED] SAR444881. The SAR444881 infusion will start at least [REDACTED] minutes [REDACTED] [REDACTED] For Dose Optimization Cohort A1 the dosing sequence is as follows: [REDACTED] [REDACTED] [REDACTED] Only premedication for [REDACTED] planned on Day 1 should be given [REDACTED], as the full premedication should start 7 days before Day 1.

For Part 2, the maximum duration of treatment will not exceed 2 years.

5.1.2.1 Part 1: SAR444881 Dose Escalation

In the dose escalation part, the dose of SAR444881, given alone and in combination with pembrolizumab or with cetuximab, will be escalated to determine the MTD (or MAAD, if no MTD is reached) of SAR444881.

SAR444881 Monotherapy Dose Escalation (Sub-Part 1A): SAR444881 will be administered to participants in escalating doses – each participant will be administered SAR444881 Q2W at one of the following planned dose levels: 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, or 20 mg/kg. Participants will be assigned to a dose level in the order of study entry. Up to 60 participants will be treated in Sub-Part 1A.

SAR444881 Combinations Dose Escalation (Sub-Parts 1B/1C): SAR444881 will be administered in escalating doses in combination with pembrolizumab (Sub-Part 1B) or with cetuximab (Sub-Part 1C). Pembrolizumab and cetuximab will be administered at their recommended dosage. The two sub-parts will enroll in parallel and will start enrolling participants once a decision has been made to escalate SAR444881 to the 3 mg/kg dose level or once an MTD of lower than 3 mg/kg has been established in Sub-Part 1A. Sub-Parts 1B and 1C may start enrolling participants after a decision has been made to escalate SAR444881 to a higher dose level than 3 mg/kg dependent on Sub-Part 1A available safety data, e.g. occurrence of DLTs at 0.1 mg/kg, 0.3 mg/kg, or 1 mg/kg.

The starting dose of SAR444881 in Sub-Part 1B will be 1 mg/kg or one dose level below the established SAR444881 monotherapy MTD, the lower of the two. The dose of SAR444881 will be escalated up to SAR444881 monotherapy MTD (or MAAD, if no MTD is reached) following the same escalation scheme of Sub-Part 1A and all participants will receive 200 mg of pembrolizumab

Q3W. SAR444881 will be administered Q3W.

In Sub-Part 1C, the starting dose of SAR444881 will also be 1 mg/kg or one dose level below the established SAR444881 monotherapy MTD, the lower of the two. The dose of SAR444881 will be escalated up to SAR444881 monotherapy MTD (or MAAD, if no MTD is reached) following the same escalation scheme of Sub-Part 1A. All participants will receive cetuximab at a dose of 500 mg/m² Q2W. Premedication with a [REDACTED] will be given prior to each cetuximab dosing. SAR444881 will be administered Q2W.

Participants will be assigned to a dose level in the order of study entry. Up to 48 participants will be treated in Sub-Parts 1B and 1C each across four planned dose levels.

Dose escalation will follow a standard “3 + 3” design [217] as outlined in [Figure 1](#). All participants in Part 1 will be treated until meeting criteria for treatment discontinuation as detailed in [Section 8.1](#).

“3 + 3” dose escalation in the three sub-parts will follow its conventional design: 3 participants will be enrolled in each dose level cohort unless a DLT occurs, in which case the cohort will be expanded to 6 participants. If no additional DLT is observed in the expanded cohort, the next higher dose cohort will be opened for enrollment. Any cohort with ≥ 2 DLT out of 3 or 6 evaluable participants will have surpassed the MTD. The next lower dose cohort will be determined to be the MTD once it has been determined that no more than 1 of 6 participants has experienced a DLT. (note: if the next lower dose cohort only contains 3 participants, then 3 additional participants will be enrolled to have a total of 6 DLT evaluable participants at the MTD). The SAR444881 dose in combination cohorts will be escalated to a higher dose level only after the higher dose was evaluated in the corresponding Sub-Part 1A single agent dose escalation cohort and was determined to be safe by the SRC.

A staggered dosing approach will be used in the three dose escalation sub-parts. The first participant to be dosed at Cycle 1 Day 1 of each dose level will be observed for a minimum of 72 hours before additional participants (i.e., participant 2 onward in that cohort) receive study treatment at the same dose level.

DLTs will be assessed over a 4-week period from the start of treatment. Escalation to the next cohort will only commence after a 4-week DLT observation period, beginning from the first study drug administration of the last participant of each dose level cohort. If no DLTs are encountered in the 4-week DLT observation period, then the next cohort will be started, and the same pattern repeated. Participants who received <90% of the SAR444881 infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be considered evaluable for dose escalation decisions and will need to be replaced. Prior to dose escalation, the available safety data for all participants treated in the study to date, including the current dose cohort, will be evaluated by a SRC consisting of one or more independent oncology experts with substantial experience in the use of immunomodulatory oncology drugs, Principal Investigators, the study’s Medical Monitor, a Sponsor employee responsible for the clinical study (or a Sponsor designee), and additional experts if required. Additional details on the SRC can be found in [Section 5.1.5](#).

Intra participant dose escalation of SAR444881 is allowed for participants enrolled to Sub-Part 1A 0.1 mg/kg and 0.3 mg/kg dose level cohorts. Escalating the participant’s SAR444881 dose to the next dose level may occur only once the higher dose level has been defined as safe by the SRC and a

Participants with insufficient data to establish safety during the 4-week DLT evaluation period or those who withdraw from the study during the DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level upon agreement of the Sponsor/Medical Monitor and Investigators. The incidence of DLT(s) during the 4-week DLT evaluation period will be used in dose escalation decisions and to define the MTD (or MAAD, if no MTD is reached) and the recommended dose of SAR444881 as a single agent and in combination with pembrolizumab or with cetuximab. AEs occurring after the 4-week DLT period will be considered for the purposes of defining the recommended dose(s) upon agreement between the Sponsor and the SRC.

Once the tolerability (during the DLT evaluation) of a given SAR444881 dose of 1 mg/kg and above in either Sub-Part 1A, 1B, or 1C has been established, up to 6 additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles of SAR444881 administered alone or in combination with pembrolizumab or with cetuximab.

The recommended dose(s) of SAR444881 as a single agent and in combination with pembrolizumab or with cetuximab will be determined at the end of each dose escalation sub-part through analysis of all the available relevant data including, but not limited to, safety information, the MTD (or MAAD, if no MTD is reached), efficacy data, pharmacokinetics, and pharmacodynamic data. The recommended dose(s) of SAR444881 as a single agent and in combination with either pembrolizumab or cetuximab will be decided by the Sponsor and approved by the SRC prior to initiation of enrollment of optimization/expansion phase (Part 2) participants. The recommended dose(s) of SAR444881 as a single agent and in combination may differ dependent on regimen-specific data collected in the three dose escalation sub-parts. At least two recommended doses will be selected for SAR444881 when in combination with pembrolizumab or with cetuximab.

The SAR444881 Monotherapy and Combination recommended dose(s) will not exceed the MTD, defined as the highest dose in each Part 1 sub-part in which no more than 1 of 6 participants experienced a DLT. If an MTD has not been reached, the recommended dose(s) will not exceed each sub-part's MAAD. Incidence of adverse events not meeting the definition of DLTs may also be considered when determining the recommended dose(s).

██████████ of potential SAR444881 biological effects will be studied in Part 1 using pre- and on-treatment ██████████. Studied ██████████ will include the following ██████████ that were identified in preclinical *in vitro* and *in vivo* mouse models to correlate with the anti-tumor effect of SAR444881:

[REDACTED]

[REDACTED]

Efficacy assessments of the anti-tumor activity of SAR444881 as a single agent and in combination will be completed for all Part 1 participants and will be based on tumor measurements, using RECIST v1.1. Changes in tumor volume, regardless of meeting criteria for an objective response, and changes in PD immune activation markers may guide selection of recommended dose(s) and may support defining a recommended dose(s) that is lower than the MTD or MAAD.

Part 1 of the study will assess the pharmacokinetics (PK) of SAR444881 and will include multiple collections of pre-dose, end-of-infusion, and post-infusion samples to determine SAR444881 serum concentrations versus time data. Blood samples will also be evaluated for ILT2 receptor occupancy (RO) in monocytes and CD8 and NK cells at the different escalation dose levels. PK and RO data collected in the dose escalation phase along with preclinical serum concentration data from mouse tumor efficacy models and RO data from *in vitro* assays may also be taken into consideration when determining the recommended dose(s) of SAR444881.

5.1.2.2 Part 2: SAR444881 Dose Optimization/Expansion

The purpose of the SAR444881 dose optimization (Part 2A) is to gather preliminary anti-tumor activity information on SAR444881 in combination with pembrolizumab, cetuximab, and/or chemotherapy in specific patient populations and gather additional safety, tolerability, PK, and pharmacodynamic information in order to define the optimal dose of SAR444881. The purpose of the SAR444881 dose expansion (Part 2B) is to gather preliminary anti-tumor activity information on SAR444881 as a monotherapy. The preliminary anti-tumor activity of SAR444881 will be assessed in select populations with tumor types known to express HLA-G – Part 2 will consist of five cohorts enrolling gastric or gastroesophageal junction adenocarcinoma, colorectal carcinoma, or non-small cell lung cancer patients with advanced disease.

Part 2 of the study will start enrolling participants at stage 1 after the recommended dose(s) of SAR444881 have been determined based on data from each sub-part of the dose escalation phase. For Cohorts A1 and B1 enrollment will commence once the recommended dose(s) of SAR444881 have been determined in Sub-Part 1B. For Cohort C1 and E1, enrollment will commence once the recommended dose(s) of SAR444881 have been determined in Sub-Part 1C. For Cohort D1, enrollment will commence once the recommended dose(s) of SAR444881 have been determined in Sub-Part 1A. Doses chosen for dose optimization (Part 2, Stage 1) are described in [Section 3.2.7](#).

[REDACTED]

Participants in Part 2 will be allowed to continue study treatment until the first occurrence of any of the following:

- Progressive Disease (PD) defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see [Appendix 7](#)) unless participant meets criteria for treatment beyond progression (see [Section 5.1.4](#))
- Clinical deterioration suggesting that no further benefit from treatment is likely
- Intolerance to therapy
- Participant meets criteria for discontinuation of study treatment as outlined in [Section 8.1](#)

For additional details on number of participants, study population, and enrollment scheme please refer to [Sections 5.2, 6, and 11.1.2](#) respectively.

Continuous evaluation of toxicity events will be performed throughout enrollment for all optimization/expansion cohorts. If, at any time, the aggregate rate of treatment-emergent adverse events at least possibly related to any drug in the trial treatment regimen meeting DLT criteria exceeds 25% across all participants treated in optimization/expansion cohorts, further enrollment will be interrupted, and the findings will be discussed by the SRC. Enrollment will resume only after a safety analysis has been completed by the SRC and the Sponsor. Participants who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another participant will not be automatically precluded from continued dosing during the safety review and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review. Depending on the nature and grade of the toxicity, and after assessing the risk/benefit ratio, then an alternate dose level may be evaluated.

If 3 cases of deaths or treatment emergent life-threatening serious adverse events, considered at least possibly related to any drug in the trial treatment regimen, occur in a dose optimization/expansion cohort, further enrollment to the cohort will cease and enrollment to other optimization/expansion cohorts will be interrupted. The findings will be shared with regulatory authorities and Institutional Review Boards/Independent Ethics Committees (IRB/IEC) and promptly discussed by the SRC. The SRC will review the available safety data for all participants treated to date in the study, consider whether study drug should be discontinued in all participants including those tolerating study treatment, consider if any protocol amendments are required to assure participant safety including revising inclusion or exclusion criteria, and discuss the risk-benefit balance of resuming enrollment. Enrollment will resume only upon recommendation by the SRC and after approval by regulatory authorities and IRB/IEC according to applicable local regulations.

5.1.2.3 Safety Run-In (Cohort A1)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.1.3 Safety Follow Up Period

Once the decision is made to discontinue the participant from treatment, all participants will enter a safety follow up period. An end of treatment (EOT) visit will be completed for all participants and this visit will be considered the start of the safety follow up period. An on-treatment visit may be considered an EOT visit if all EOT assessments, specified in the Schedule of Activities ([Section 2](#)) and [Section 10.7](#), have been performed at that visit, otherwise a separate EOT visit should be completed.

After the EOT visit, all participants will be evaluated for any new AEs for at least [REDACTED] after the last dose of study treatment. Follow up visits should occur at Days 30, 60, and 90 (± 7 days for each visit) after the date of SAR444881 discontinuation in single agent cohorts and after SAR444881, pembrolizumab, cetuximab, pemetrexed, or carboplatin discontinuation in combination cohorts (the latest of the two administered study drugs if one drug is discontinued earlier than the other). All participants will be required to complete the clinical safety follow up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation. Participants with an ongoing AE, at least possibly related to study drug, should continue to be followed until resolution, stabilization or the AE is deemed irreversible. See [Section 10.2.1](#) for reporting of AEs that occur after the safety follow-up period.

For additional information on procedures and assessment to be completed in the safety follow up period see [Table 2-6](#).

5.1.4 Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed in conventional chemotherapy. Accumulating clinical evidence indicates some participants treated with immune system stimulating agents may develop disease progression by the conventional response criteria before demonstrating clinical objective responses and/or stable disease [218]. These patients may derive clinical benefit despite initial evidence of progressive disease.

Two distinct non-conventional patterns have been reported for immunotherapies: 1) a reduction in target tumor burden despite the appearance of new lesion(s), and 2) a transient increase in target

tumor burden in an initial phase, followed by subsequent tumor shrinkage. Two hypotheses explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study drug that might induce a non-conventional response pattern in some participants.

Treatment beyond initial evidence of RECIST v1.1 defined progressive disease (PD) will be allowed. The decision will be based on the investigator's clinical assessment and must be approved with the Medical Monitor and documented in the study records. No additional anti-cancer therapies should be administered for the duration of the treatment beyond progression. Participants will be permitted to continue treatment with SAR444881 and with SAR444881 in combination with pembrolizumab or with cetuximab beyond initial apparent RECIST v1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Participant is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
- Participant provides written informed consent prior to receiving additional study treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities ([Section 2](#)). Radiographic assessment/scan(s) should also continue in accordance with the schedule of events for the duration of the treatment beyond progression. It is at the discretion of the Investigator to perform more frequent tumor imaging assessments. The Investigator should assure that the participant meets all treatment beyond progression criteria listed above prior to any additional study drug administration.

For participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). For the purpose of participant management, any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate

an absolute increase of at least 5 mm.

5.1.5 Safety Review Committee

A Safety Review Committee (SRC) will be set up and convene at regular intervals. It will act in an advisory capacity to the Sponsor and will monitor participant safety and evaluate the available preliminary efficacy data for the study. The SRC will consist of one or more independent oncology experts with substantial experience in the use of immunomodulatory oncology drugs and Phase 1 clinical trials, Principal Investigators, the study's Medical Monitor, a Sponsor employee responsible for the clinical study (or a Sponsor designee), and additional experts if required, e.g. a clinical pharmacologist. The SRC will provide oversight of safety, monitor actual or potential issues related to participant safety that could result in a change in the medical risk-benefit balance associated with the use of study treatment, provide preliminary efficacy considerations and provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study.

SRC responsibilities include, but are not limited to:

- Evaluating available safety data for all participants treated in the study prior to dose escalations and approving opening enrollment to next higher dose level cohort in both Part 1 and Sub-Part 2A, Cohort A1
- Identifying treatment-emergent AEs (TEAEs) that in the opinion of the SRC are of clinical significance such that further dose escalation would expose participants to unacceptable risk
- Evaluating whether a reported AE not meeting the definition of a DLT should be considered as one
- Considering the appropriate SAR444881 recommended dose(s) prior to initiation of enrollment in the dose optimization/expansion phase
- Evaluating all available ECG data at the end of the dose escalation phase for any safety issues that might require altering ECG monitoring of dose optimization/expansion phase participants
- Recommending suspension of participant enrollment or stopping the trial for safety concerns

5.2 Number of Participants

The study will enroll up to 456 participants.

Part 1 (SAR444881 Escalation): The sample size for Part 1 of this study was determined by clinical rather than statistical considerations. Specifically, the final number of participants enrolled in the study will depend on empirical safety (DLT) observations. Up to 60 participants will be treated in Sub-Part 1A (SAR444881 single agent dose escalation) and up to 48 participants in Sub-Part 1B and in Sub-Part 1C each (SAR444881 combinations escalation). These numbers reflect the maximum number of participants in each dose level described in the study's standard "3 + 3" design plus additional participants enrolled to better characterize the safety, PK, and pharmacodynamic profiles of SAR444881 (see [Section 5.1.2.1](#)). Up to 156 participants will be treated in the dose escalation phase.

Part 2 (SAR444881 Dose Optimization/Expansion Cohorts): Up to 300 participants are planned to be treated in the SAR444881 dose optimization/expansion phase. For the four indications in Sub-Part 2A, up to 60 participants for each indication will be enrolled (20 patients in Stage 1 [preliminary

efficacy assessment] and 40 patients in Stage 2 ([randomization])). For the single dose expansion cohort in Sub-Part 2B, up to 40 participants will be enrolled. This number of participants was determined in order to meet Part 2 objectives of assessing preliminary SAR444881 anti-tumor activity and optimal dose of SAR444881 in the specific tumor types enrolled in the study.

For more details on the sample size justification, see [Section 11](#).

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities ([Section 2](#)) for the last participant. For Part 1, the primary study completion is defined as the final date on which data for the primary endpoints are expected to be collected. For Part 2, the primary analysis cut-off date will be the date approximately 9 months (based on data maturity) after the last participant's last treatment in the study cohort or discontinuation of the treatment early, whichever comes first. The study cut-off date will be when the last cohort has reached its cut-off date.

6 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the Medical Monitor before enrolling the participant to the study.

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1. Signed Written Informed Consent

1. Participants must have signed and dated an Institutional Review Board/Independent Ethics Committee approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.
2. Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
3. All single agent dose escalation (Sub-Part 1A) participants treated at SAR444881 dose levels equal and greater than 1 mg/kg (≥ 1 mg/kg) and all combination dose escalation (Sub-Parts 1B/1C) and dose optimization/expansion phase (Part 2) participants with low risk biopsies (i.e., expected rate of major complications $<0.5\%$, e.g., blood, bone marrow, skin, and superficial masses; Part 2 only) must consent and will be required to undergo mandatory pre- and on-treatment biopsies. In Part 2, participants with low risk biopsies who either do not consent to a pre-treatment tumor biopsy or do not have accessible qualifying lesions are not eligible. Moderate risk biopsies (i.e., expected rate of major complications 0.5 - 1.5% , e.g., intra-abdominal, some intrathoracic, and low risk procedures in patients with increased risk of bleeding or infection) are optional, and not mandatory (Part 2 only). High risk biopsies (i.e., expected rate of major complications $>1.5\%$) are not acceptable in this trial based on the current trial objectives (Part 2 only).
4. If a participant had a biopsy in the 90 days preceding informed consent signature with no intervening anti-cancer therapy, enrollment is allowed without needing a repeat biopsy

after discussion with the Medical Monitor and availability of FFPE blocks or unstained slides as delineated in the Laboratory Manual. Participants will however be required to undergo on-treatment biopsy at acceptable clinical risk as judged by the investigator. If a participant declines to undergo the on-treatment biopsy after study drug treatment has started, the missing biopsy will not be considered a protocol deviation.

The screening, on-treatment, and upon progression biopsies will follow the same guidance methodology for sample collections, processing, and submission provided in the Laboratory Manual. See Inclusion Criterion 2 (j) **Sub-Part 2A (SAR444881 Dose Optimization) Tumor Types** and (k) **Sub-Part 2B (SAR444881 Dose Expansion Cohort D1) Tumor Types** for further details of provision of tumor tissue for dose optimization/expansion (Part 2).

2. Type of Participant and Target Disease Characteristics

1. Patients with unresectable or metastatic disease who are refractory to or are not candidates for standard approved therapy (*all sub-parts and cohorts aside from Dose Optimization Cohort A1; Cohort A1 participants remain eligible to receive standard approved therapy*)
 - i. Participants with MSI-high (MSI-H) and/or MMR-deficient (dMMR) tumors or with tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] tumors should have received pembrolizumab or another anti-PD-1 or anti-PD-L1 therapeutic antibody, if are available as part of the local standard of care, prior to enrollment into this study
2. Participants must have histologic confirmation of malignancy
3. Participants must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see [Appendix 7](#)).
4. All single agent dose escalation (Sub-Part 1A) participants treated at dose levels equal and greater than 1 mg/kg (≥ 1 mg/kg) and all combination dose escalation (Sub-Parts 1B/1C) and dose optimization/expansion phase (Part 2) participants must have at least one lesion accessible for biopsy
5. Eastern Cooperative Oncology Group Performance Status (ECOG) of 0 or 1 (see [Appendix 5](#))
6. Estimated life expectancy of more than 3 months
7. Sub-Part 1A (SAR444881 Monotherapy Dose Escalation) Tumor Types:
 - i. Breast cancer, cervical cancer, colorectal cancer, adenocarcinoma or squamous cell carcinoma of the esophagus, gastric or gastroesophageal junction adenocarcinoma, squamous cell carcinoma of the head and neck, hepatobiliary cancers (hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma), non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the skin, or urothelial carcinoma
8. Sub-Part 1B (SAR444881 in Combination with Pembrolizumab Dose Escalation) Tumor Types:
 - i. Cervical cancer, colorectal cancer, gastric or gastroesophageal junction adenocarcinoma, squamous cell carcinoma of the head and neck, hepatobiliary cancers (hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma), adenocarcinoma or squamous cell carcinoma of the esophagus, non-small cell lung cancer, pancreatic adenocarcinoma, renal cell carcinoma, squamous cell carcinoma of the skin, triple negative breast cancer, or urothelial carcinoma

9. Sub-Part 1C (SAR444881 in Combination with Cetuximab Dose Escalation) Tumor Types:
- i. K-Ras wild-type colorectal cancer (right and left-sided tumors), squamous cell carcinoma of the head and neck, hepatobiliary cancers (hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma), non-small cell lung cancer, ovarian cancer
1. Participants with BRAF-mutant colorectal cancer are eligible for enrollment
- ii. Participants with prior exposure to EGFR inhibitors (including cetuximab) are allowed to enroll
10. Sub-Part 2A (SAR444881 Dose Optimization) Tumor Types:
- i. Cohort A1:
 1. Histologically or cytologically confirmed diagnosis of Stage IV (per American Joint Committee on Cancer [AJCC] 8th edition [1]) non-squamous NSCLC,
 2. Prior anticancer therapy: 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
 - ii. Cohort B1:
 1. Histologically or cytologically confirmed diagnosis of GC or Siewert Type 2 & 3 GEJ.
 2. Participants must have MSI status known, determined locally and must have non-MSI-H disease to be eligible.
 3. Participants with unknown HER2/neu status must have their HER2/neu status determined locally. Participants previously treated with a trastuzumab-based regimen must have documentation of disease progression to be eligible.
 4. Prior anticancer therapy: Participants should have received at least one prior line of treatment, including an anti-PD-1/PD-L1 containing regimen and have progressed after a primary or secondary resistance to an anti-PD-1/PD-L1.
 - i. Cohort C1:
 1. Histologically or cytologically confirmed diagnosis of colorectal cancer. Only participants with non-MSI-H disease are eligible.
 2. MSI status: Participants must have MSI status known or determined locally and must have non-MSI-H disease to be eligible.
 3. Participants with RAS-mutant and BRAF-mutant colorectal cancer are eligible for enrollment.
 4. Prior anticancer therapy: Participants should have failed or relapsed on at least 1 regimen.
 - a. Participants with RAS wildtype colorectal cancer should have either failed or relapsed on or be ineligible for treatment with 5-fluorouracil, irinotecan, oxaliplatin, bevacizumab and anti-EGFR.
 - b. Participants with RAS-mutant colorectal cancer are eligible for enrollment; participants with RAS-mutant disease should have either failed or relapsed on or be ineligible for bevacizumab treatment.
 - c. Participants with BRAF-mutant colorectal cancer are eligible for enrollment; participants should have either failed or relapsed on treatment or be ineligible for treatment with encorafenib or other BRAF targeted therapies.

- d. Once 10 participants that previously have not been exposed to cetuximab or other anti-EGFR therapy have been enrolled, enrollment will be limited to patients who have received cetuximab or other anti-EGFR therapy as part of their last line of treatment.

- ii. Cohort E1

1. Histologically or cytologically confirmed NSCLC, Stage IV (per American Joint Committee on Cancer [AJCC] 8th edition [1]). Up to 10 participants with non-squamous NSCLC will be enrolled in Part 2, Stage 1, with the remaining enrollment allocated to patients with squamous NSCLC.
2. Prior anticancer therapy: Participants should have failed or relapsed on at least 1 prior regimen.
3. Participants with known driver alterations which include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Proto-oncogene tyrosine-protein kinase (ROS), BRAF, or RET mutation are eligible for inclusion. Participants with driver mutations must have failed or relapsed on or are ineligible for available targeted therapies.

11. Sub-Part 2B (SAR444881 Dose Expansion Cohort D1) Tumor Types:

1. Histologically or cytologically confirmed advanced cholangiocarcinoma.
2. Participants must have received and progressed/been intolerant of at least 1 prior systemic therapy for metastatic and/or unresectable disease for whom all standard of care therapies have failed.

3. Physical and Laboratory Findings

1. Participants must have adequate organ function as defined by the following:
 - i. Lymphocyte count $\geq 500/\text{mm}^3$
 - ii. Neutrophil count $\geq 1,500/\text{mm}^3$
 - iii. Platelet count $\geq 100,000/\text{mm}^3$
 - iv. Hemoglobin concentration $\geq 9.0\text{g/dL}$
 - a. Criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin ($\geq$ approximately 3 months).
 - v. AST and ALT $\leq 2.5 \times \text{ULN}$ or $\leq 5.0 \times \text{ULN}$ in patients with hepatocellular carcinoma, cholangiocarcinoma or if liver metastases are present
 - vi. Total bilirubin $\leq 1.5 \times \text{ULN}$ (except participants with Gilbert Syndrome who must have a total bilirubin level of $< 3.0 \times \text{ULN}$)
 - vii. Creatinine clearance (observed or estimated using the Cockcroft–Gault equation) $\geq 45 \text{ mL/min}$ (Cohorts A1 and D1 only)

4. Tumor biopsies:

1. Dose Escalation:
 - i. Participants in SAR444881 monotherapy dose escalation 0.1 mg/kg and 0.3 mg/kg dose level cohorts will be asked for their consent for optional pre- and on-treatment biopsies for performance of correlative tissue studies
 - ii. All other participants must consent and will be required to undergo mandatory

pre- and on-treatment biopsies for performance of correlative tissue studies

iii. All participants will be asked for optional end of treatment biopsy

2. Dose Optimization/Expansion:

- i. **Mandatory baseline biopsy** for participants with low risk biopsies (i.e., expected rate of major complications <0.5%, e.g., blood, bone marrow, skin, and superficial masses) in **all dose optimization/expansion cohorts**: Tissue must be available for submission to the Sponsor. If sufficient sample is not available from biopsies collected in the last 6 months with no intervening therapy prior to consent, then the patient must be willing and able to undergo a biopsy for this collection.
- ii. Moderate risk biopsies (i.e., expected rate of major complications 0.5-1.5%, e.g., intra-abdominal, some intrathoracic, and low risk procedures in patients with increased risk of bleeding or infection) are optional, and not mandatory. High risk biopsies (i.e., expected rate of major complications >1.5%) are not acceptable in this trial based on the current trial objectives.
- iii. **On-treatment biopsy** for at least 20 participants in **all dose optimization/expansion cohorts**, if clinically feasible but may be optional before 20 biopsies have been obtained based on the totality of data at the sole discretion of the Sponsor.
- iv. If imaging is required to obtain biopsy material, the biopsy should be performed using ultrasound guidance if feasible to prevent additional study-related radiation dose.

5. **Age and Reproductive Status**

1. Males and Females, at least 18 years old
2. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment.
3. Women must not be breastfeeding
4. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception ([Appendix 4](#)) for the duration of treatment with study treatment and 10 months duration after last dose of study drug
5. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.
6. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception ([Appendix 4](#)) for the duration of treatment with study treatment and 7 months duration after the last dose of study drug. In addition, male participants must be willing to refrain from sperm donation during this time.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception ([Appendix 4](#)), which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1. Medical Conditions

1. Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
2. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses < 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease
3. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (i.e., without evidence of progression) for at least 4 weeks by repeat imaging (Note: The repeat imaging should be performed during study screening.), clinically stable, and without requirement of steroid treatment for at least 14 days before the first dose of study intervention.
4. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
5. Non-hepatocellular carcinoma participants: acute or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
6. Hepatocellular carcinoma participants: untreated active hepatitis B virus or dual infection with HBV/HCV or other hepatitis combinations or decompensated cirrhosis (Child Pugh B8 and higher)
7. Prior non-hematological malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
8. Prior hematological malignancy active within the previous 5 years
9. Participants after solid organ or allogeneic hematopoietic stem cell transplant
10. History of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting co-stimulation of immune cells or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g. hormone replacement after adrenal crisis)
11. History of Grade 3 or 4 infusion reaction, Grade 3 or 4 neurological toxicity, Grade 2, 3 or 4 myocarditis, Grade 4 nephritis, AST or ALT increases to more than 8 times ULN or total bilirubin increases to more than 3 times ULN, or Grade 4 colitis related to prior pembrolizumab or other anti-PD(L)-1 antibodies (for Sub-Part 1B, and Part 2 Cohorts A1 and B1)
12. History of life-threatening toxicity, Grade 3 or 4 infusion reaction, or three or more occurrences of Grade 3 or 4 dermatologic toxicity related to prior cetuximab or other anti-EGFR antibodies (for Sub-Part 1C, and Part 2 Cohorts C1 and E1)
13. History of clinically significant hypomagnesemia, hypocalcemia, or hypokalemia related to prior cetuximab or other anti-EGFR antibodies (for Sub-Part 1C, and Part 2 Cohorts C1 and E1)
14. History of Grade 2 or higher pneumonitis or interstitial lung disease
15. Unstable or deteriorating cardiovascular disease within the previous 6 months prior to screening including but not limited to the following:

- i. Unstable angina or myocardial infarction;
 - ii. Transient ischemic attack (TIA)/cerebrovascular accident (CVA);
 - iii. Congestive heart failure (New York Heart Association [NYHA] Class III or IV);
 - iv. Uncontrolled clinically significant arrhythmias or arrhythmias requiring medication for rate control.
16. Any major surgery within 4 weeks of study drug administration. Participants must have recovered from the effects of major surgery at least 14 days before the first dose of the study drug
17. Any condition (including medical, emotional, psychiatric, or logistical) that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of study results

2. Prior/Concomitant Therapy

1. Immunosuppressive agents or immunosuppressive doses of systemic corticosteroids (except as permitted in the study protocol)
2. Cytotoxic anti-cancer agents, unless at least 4 weeks have elapsed from last dose of prior anti-cancer therapy and initiation of study therapy
3. Non-cytotoxic anti-cancer agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study therapy
4. Use of other investigational drugs (drugs not marketed for any indication) within 28 days before first study drug administration
5. Prior immune therapy treatments (for example, but not limited to: anti-CTLA4, anti-PD-L1, anti-PD-L2, anti-PD-1, IL-2), unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of immune therapy and initiation of study therapy
6. Prior treatment with macrophage or NK cells activating therapies, e.g. drugs targeting CD-47, SIRP α , KIR, NKG2A
7. Inability to comply with restrictions and prohibited treatments as listed in [Section 7.10 Concomitant Therapy](#)
8. Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to study drug administration. Refer to [Section 7.10.1](#) for prohibited therapies
9. Administration of a live attenuated vaccine within 28 days prior to the first dose of study therapy
10. Antibiotic use (excluding topical antibiotics) ≤ 14 days prior to first dose of IMP, or any serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV or oral antibiotics
11. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis.

Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

3. Allergies and Adverse Drug Reaction

1. History of allergy or hypersensitivity to study drug components

2. Has severe hypersensitivity ($\geq$ Grade 3) to pembrolizumab and/or any of its excipients.
3. History of any clinically significant drug allergy (such as anaphylaxis, hepatotoxicity, or hypersensitivity reactions) to other monoclonal antibodies

4. Pregnancy Exclusion

1. A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5. SAR444881 Dose Optimization (Sub-Part 2A):

1. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.

2. Cohort A1:

- i. Known driver alterations which include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Proto-oncogene tyrosine-protein kinase (ROS)1, BRAF, or RET mutation for participants with non-squamous NSCLC.
- ii. 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).
- iii. Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose $\leq$ 1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

3. Cohorts A1 and E1:

- i. Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of trial treatment.

4. Cohort C1:

- i. Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD 1/PD-L1 but have written confirmation they were on control arm are allowed).
- ii. The patient has clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months or high risk of uncontrolled arrhythmia or uncontrolled cardiac insufficiency.
- iii. The patient has uncontrolled or poorly controlled hypertension (>180 mmHg systolic or >130 mmHg diastolic).
- iv. The patient has a history of allergic reactions attributed to compounds of chemical or biologic composition similar to those of cetuximab, or if the patient had red meat allergy/tick bite history.

6.3 Screen Failures

Screen failures are defined as participants who consent to participate in the study but who are not subsequently entered in the study/included in the analysis population. 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, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4 Retesting During Screening Period

Participant re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (i.e. participant has not been treated). If re-enrolled, the participant must be re-consented, but does not require a new Subject Number.

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value). Any new result will override the previous result and is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in [Table 2-1](#) Screening Procedural Outlines may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Auxiliary Medicinal Product (AxMP).

An Investigational Product (IP), also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, the investigational medicinal products are SAR444881, pembrolizumab, cetuximab, carboplatin, and pemetrexed. IPs' description and storage information are described in [Table 7-1](#).

Table 7-1: Study Treatments for TCD17465

Product Description / Class and Dosage Form	Potency	IP/ AxMP	Blinded or Open Label	Packaging	Storage Conditions (per label)
SAR444881 Solution for Infusion	■ mg/mL (■ mg/vial)	IP	Open Label	20 mL glass vial	Store at 2-8° C
Pembrolizumab Solution for Infusion	100 mg/4 mL (25 mg/mL) or as per locally approved formulation	IP	Open Label	4mL vial May be sourced locally when necessary (Part 1 only)	Refer to the label or Pharmacy Manual

Cetuximab Solution for Infusion	200 mg/100 mL (2 mg/mL) (US and Canada only) or 500 mg/100 mL (5 mg/mL) or as per locally approved formulation	IP	Open Label	100mL vial May be sourced locally when necessary	Refer to the label or Pharmacy Manual
Carboplatin	450 mg/45 mL vial concentrate for solution for infusion (10mg/mL) Or As per locally approved formulation	IP	Open Label	45 mL vial Or To be sourced locally where possible. Central sourcing (EU sourced and clinically labeled) only for the countries where local sourcing is not possible	Refer to the label or Pharmacy Manual
Pemetrexed	500 mg powder for concentrate for solution for infusion Or 500mg/20 mL concentrate for solution for infusion vial (25mg/mL) Or As per locally approved formulation	IP	Open Label	Vial Or To be sourced locally where possible. Central sourcing (EU sourced and clinically labeled) only for the countries where local sourcing is not possible	Refer to the label or Pharmacy Manual
Diphenhydramine (ATC Code: R06AA02)	As per locally approved formulation	AxMP	Open Label	To be sourced locally	Refer to the label
Folic Acid (ATC Code: B03BB01)	As per locally approved formulation	AxMP	Open Label	To be sourced locally	Refer to the label
Vitamin B12 (ATC Code: B03BA01)	As per locally approved formulation	AxMP	Open Label	To be sourced locally	Refer to the label
Dexamethasone (ATC Code: H02AB02)	As per locally approved formulation	AxMP	Open Label	To be sourced locally	Refer to the label

ATC: Anatomical Therapeutic Chemical

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as AxMP.

7.1 Packaging and Labeling

The study drug will be packaged and labeled according to current Good Manufacturing Practice (GMP) guidelines. Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.2 Ordering Study Treatment

For Part 1: Study drug supplies may be requested by completing a Drug Supply Request Form and faxing or e-mailing the form to the Drug Supply Coordinator at the Sponsor. Refer to the Study Contact Information list for contact details.

For Part 2: an IRT system will be used to facilitate drug supply ordering. Directions for the IRT will be provided to each site in the pharmacy manual prior to Part 2 start.

7.3 Storage/Preparation/Handling

SAR444881 vials must be stored at a temperature of 2°C to 8°C and should be kept in their original cartons. After SAR444881 has been prepared for administration, the total storage time from the start of dose preparation to the completion of IV infusion is not to exceed 24 hours at 2-8°C or 6 hours at ambient room temperature. Storage and handling of pembrolizumab and cetuximab should be in accordance with their Prescribing Information. See the Pharmacy Manual or pembrolizumab or cetuximab Prescribing Information for more detailed information.

The product storage manager (or designee) should ensure that the study drug is stored in accordance with the environmental conditions, e.g. temperature, as determined by Sanofi. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact Sanofi immediately.

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

For study treatment not provided by Sanofi and obtained commercially by the site, storage should be in accordance with the product label.

Investigational product documentation (whether supplied by Sanofi or not) that includes all processes required to ensure drug is accurately administered must be maintained. This includes documentation of drug storage, administration and, as applicable, storage temperatures, dilutions, and use of required processes (e.g. required diluents, administration sets).

Care must be taken to assure sterility of the prepared SAR444881 solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between SAR444881 and polyolefin bags have been observed.

Recommended safety measures for preparation and handling of SAR444881 include laboratory coats and gloves.

Stability data for SAR444881 following transfer to and dilution in the IV bag support [REDACTED] hours at room temperature however as SAR444881 does not contain preservatives the SAR444881 diluted solution should be used within [REDACTED]

Please refer to the current version of the Pharmacy Manual for complete preparation and handling information of SAR444881. See the Pharmacy Manual or Prescribing Information for pembrolizumab and cetuximab preparation information.

7.4 Treatments Administered

The selection and timing of dose for study participants is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Dosage level(s)	Frequency of Administration	Route of Administration	Premedication
SAR444881	Escalation cohort Sub-Part 1A: 0.1, 0.3, 1, 3, 10 and 20 mg/kg Sub-Parts 1B/1C: 1, 3, 10, and 20 mg/kg Optimization/Expansion cohort Part 2: (Part 2, Stage 1): 10 mg/kg (all cohorts)	Sub-Parts 1A/1C and Part 2 Cohorts C1, D1, and E1: Q2W Sub-Part 1B and Part 2 Cohorts A1 & B1: Q3W	IV	Not recommended
Pembrolizumab	200 mg	Q3W	IV	Not recommended
Cetuximab	Escalation and Optimization Cohort C1 and E1: 500 mg/m ²	Q2W	IV	Refer to Section 7.4.3
Carboplatin	AUC of 5	Q3W for 4 cycles	IV	Not recommended
Pemetrexed	500 mg/m ²	Q3W	IV	Refer to Section 7.4.4.1

In combination cohorts drug administration visits, [REDACTED]. The SAR444881 infusion will start at least [REDACTED] completion of [REDACTED].

the pembrolizumab infusion and at least [REDACTED] after the cetuximab infusion.

For all study participants, SAR444881 infusions will require a [REDACTED] observation period following the completion of the infusion for the first [REDACTED] doses and a [REDACTED] observation period for all subsequent doses.

The dosing sequence for each dose optimization/expansion cohort will be as follows:

- **Cohort A1:** [REDACTED]
[REDACTED]
[REDACTED]
- **Cohort B1:** [REDACTED]
[REDACTED]
- **Cohort C1 and E1:** [REDACTED]
[REDACTED]
- **Cohort D1:** [REDACTED]

7.4.1 SAR444881 Treatment

Each participant's SAR444881 dose will be determined by the participant's weight in kilograms, which will be determined on the day of each SAR444881 dosing. If the participant's weight is within 10% of the Cycle 1 Day 1 weight, study drug doses do not need to be recalculated depending on institutional guidelines/preference.

SAR444881 is to be administered as an IV infusion, with a 0.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. SAR444881 will be infused over [REDACTED] minutes at all dosage levels except for the [REDACTED] mg/kg dosage which will be infused over [REDACTED] minutes. For all study participants, infusions will require a [REDACTED] observation period following the completion of the infusion of the first [REDACTED] doses and a [REDACTED] observation period following the completion of all subsequent doses. See [Section 10.5.3](#) for schedule of vital signs measurements during infusions. SAR444881 is not to be administered as an IV push or bolus injection.

SAR444881 infusions must be promptly followed by a flush of diluent to clear the line. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

In combination cohorts drug administration visits, combination agents [REDACTED]
[REDACTED]
[REDACTED].

Participants may be dosed within a ± 2 -day window (except Cycle 1 in the Dose Escalation phase during which any changes in timing of visits require Sponsor approval). In combination cohorts, both study drugs should be administered on the same day. [REDACTED]
[REDACTED]. Participants should be carefully monitored for infusion reactions during SAR444881 administration. If an acute infusion reaction is noted, participants should be managed according to [Section 9.4](#).

Doses of SAR444881 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose. See [Section 9.2](#) for details on SAR444881 dose delays due to toxicity.

7.4.2 Pembrolizumab Treatment

Pembrolizumab will be administered according to its recommended dosage and administration as described in its Prescribing Information.

All participants should receive pembrolizumab at a dose of 200 mg every three weeks. Pembrolizumab should be infused intravenously over [REDACTED] minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Other drugs should not be co-administered through the same infusion line. Pembrolizumab must not be administered as an intravenous push or bolus injection. In combination cohorts drug administration visits, [REDACTED]. See [Section 10.5.3](#) for schedule of vital signs measurements during infusions.

Premedications are not recommended for the first dose of pembrolizumab. Participants should be carefully monitored for infusion reactions during pembrolizumab administration. If an acute infusion reaction is noted, participants should be managed according to [Section 9.4](#).

No escalations or reductions of pembrolizumab dose are allowed. Participants may be dosed within a ± 2 -day window (except Cycle 1 in the Dose Escalation phase during which any changes in timing of visits require Sponsor approval). Doses of pembrolizumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. In the case that an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. See [Section 9.2](#) for details on pembrolizumab dose delays due to toxicity.

Care must be taken to assure sterility of the prepared solution as pembrolizumab does not contain any preservative. Further details regarding preparation and administration are provided separately in the Pharmacy Manual.

7.4.2.1 Justification for Pembrolizumab Dose

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

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

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [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 non-small cell lung cancer (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 PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 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. [REDACTED]

[REDACTED]

[REDACTED]

7.4.3 **Cetuximab Treatment**

Cetuximab will be administered according to its recommended dosage and administration as described in its Prescribing Information. For NSCLC (Cohort E1) the cetuximab dose will be 500 mg/m² IV Q2W, which is a dose that has proven safe and well tolerated in multiple studies of this disease [171].

Participants should receive cetuximab 500 mg/m² IV Q2W. Cetuximab should be infused intravenously over 120 (-5, +30) minutes through a low protein binding 0.22-micrometer in-line filter. Cetuximab must not be administered as an intravenous push or bolus injection and the infusion rate should not exceed 10 mg/min. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 0.9% solution for injection at the end of infusion. In

combination cohorts drug administration visits, cetuximab will be infused first, followed by SAR444881. See [Section 10.5.3](#) for schedule of vital signs measurements during infusions.

All participants administered cetuximab will be premedicated with a [REDACTED] 30–60 minutes prior to each cetuximab dosing. Use of other premedication protocols is allowed after discussion with the Medical Monitor. Participants should be carefully monitored for infusion reactions during cetuximab administration. If an acute infusion reaction is noted, participants should be managed according to [Section 9.4](#).

Cetuximab dosage may be modified for adverse reactions management in accordance with the drug's Prescribing Information (see [Section 9.5](#)). Participants may be dosed within a ± 2 -day window (except Cycle 1 in the Dose Escalation phase during which any changes in timing of visits require Sponsor approval). Doses of cetuximab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. In the case that an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. See [Section 9.2](#) for details on cetuximab dose delays due to toxicity.

Care must be taken to assure sterility of the prepared solution as cetuximab does not contain any antimicrobial preservative or bacteriostatic agent. Further details regarding preparation and administration are provided separately in the Pharmacy Manual.

Participants administered cetuximab should be instructed to limit sun exposure during treatment and for 2 months after the last dose of cetuximab. Prophylactic use of oral tetracyclines, topical corticosteroids and moisturizers should be considered for prevention of dermatological toxicity.

Participants presenting with signs and symptoms suggestive of keratitis such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmologist.

7.4.4 Pemetrexed Treatment

Pemetrexed will be administered after administration of pembrolizumab.

- Formulation: pemetrexed 25 mg/mL (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/m² IV infusion over approximately 10 mins until PD or unacceptable toxicity.

7.4.4.1 Pemetrexed Premedication

All participants in Cohort A1 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 [219].

7.4.5 Carboplatin Treatment

Carboplatin will be administered immediately after pemetrexed for the first 4 cycles 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.

7.5 Dosage Modification

Participants enrolled at either the 0.1 mg/kg or 0.3 mg/kg SAR444881 dose levels in the dose escalation phase (Sub-Part 1A) may be permitted to dose escalate up to 1 mg/kg in consultation and agreement by the Medical Monitor. Escalating the participant's dose to the next higher dose level, i.e. 0.1 to 0.3 mg/kg and 0.3 to 1 mg/kg, may occur only once the higher dose level has been defined as safe by the SRC and a decision has been made to further dose escalate.

Intra-participant SAR444881 dose escalation is not permitted in participants enrolled at other dose levels in the dose escalation phase or in participants of the dose optimization/expansion phase to allow better evaluation of the safety and efficacy at individual dose levels. No dose reductions of SAR444881 are allowed.

Dosage modifications of pembrolizumab are not allowed in this study. Cetuximab dosage may be modified for adverse reactions management in accordance with the drug's Prescribing Information (see [Section 9.5](#)).

7.5.1 Dosage 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 SAR444881/pembrolizumab. Similarly, participants may discontinue SAR444881/pembrolizumab and continue on chemotherapy alone if appropriate.

Recommended dose modifications for key chemotherapy toxicities are outlined in [Table 7.5-1](#), [Table 7.5-2](#), and [Table 7.5-3](#). These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Table 7.5-1 – Dose modification for chemotherapy agents

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
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/m ²	375 mg/m ²	250 mg/m ²	Discontinue

Table 7.5-2 - Recommended dose modifications for chemotherapy hematological toxicity

			Pemetrexed	Carboplatin
Platelets		ANC	Dose level (DL) from Table 7.5-1	
≥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 7.5-3 - Recommended dose modifications for chemotherapy non-hematological toxicity

		Pemetrexed	Carboplatin
Event	CTCAE V5.0 Grade	Dose level (DL) from Table 7.5-1 ^a	
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0
Neurotoxicity	Grade 2	DL 0	DL 0
	Grade 3 or 4	DL -1	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1
	Grade 4	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1

^a The dose modifications listed above are recommended for the first instance of non-hematological toxicity. In case of first recurrence of the same Grade ≥3 event: administer the next lower dose level if restart is possible. In the case of a second recurrence of the same Grade ≥3 event: permanently discontinue pemetrexed or carboplatin.

7.6 Method of Treatment Assignment, Participant Numbering

7.6.1 Method of Treatment Assignment

Enrollment to Parts 1 and 2 of the study will be managed by the Sponsor.

For Part 1: The investigative site will contact the Sponsor for treatment assignment once a participant is determined to be eligible for enrollment. Participants who meet all eligibility requirements will be assigned to a treatment group as determined by the Sponsor. Assignment to treatment groups in Part 1 (escalation dose level cohorts) will be in the order participants have completed screening. Assignment to the three dose escalation sub-parts will be managed by the Sponsor. Participant assignment will aim to assure an adequate enrollment rate across escalation sub-parts and an even sub-part assignment across participating sites. Assignment to treatment groups in Part 2 (optimization/expansion cohorts) will be according to the participant's tumor type and will be coordinated by the Sponsor.

For Part 2: Interactive Response Technology (IRT) will be used to control recruitment, assignment per site and facilitate drug supply. The site will contact the IRT prior to the start intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required.

7.6.2 Participant Numbering

Each participant is identified in the study by a Subject Number, that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial.

For Part 1: The Subject Number as assigned by the Sponsor is numbered uniquely across the entire database. Upon signing the informed consent form, the participant will be assigned to the next sequential Subject Number available through the Electronic Data Capture (EDC) system.

During part 2, the IRT will be responsible to generate the participant randomization list according to which it will allocate the treatments to the patients.

Before the part 2 is initiated, the log in information and directions for the IRT will be provided to each site.

7.7 Blinding

As this is an open-label study, blinding procedures are not applicable. The Sponsor personnel may have access to treatment information during the course of the trial to help with internal decision-making and for disclosure of preliminary scientific results.

For Part 2, the specific intervention to be taken by a participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the following steps: central randomization.

During the study, statistician might perform unblinded safety and efficacy analyses for the study board discussion. Access to these data and analyses will be available for all study board members.

7.8 Drug Accountability

Sanofi is the provider of the study drug supply. All study drug kits will be supplied to the Investigator by Sanofi or its designee. Study drug supplies must be kept

in an appropriate, secure locked area and stored in accordance with the conditions specified on the

drug labels.

The individual vial labels have a place to record participant ID and visit information. Use of each vial of study drug should be recorded on the individual vial label.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Sanofi at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

7.9 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, as well as the participant's medical records and case report form (CRF). Study drug will be administered in the clinic by trained personnel. Drug accountability should be reviewed by the site study staff at each visit.

7.10 Concomitant Therapy

Concomitant medications should be recorded at baseline and throughout the treatment of the study in the appropriate section of the CRF. Medications taken within 4 weeks prior to study drug administration must be recorded on the CRF as well.

All medications (prescription and over-the-counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the participant from Screening through End of Treatment phase will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (e.g. a biopsy) should also be included.

Any subsequent anti-cancer therapy will be recorded until end of study or death, in the appropriate section of the CRF.

Concomitant medication information will not be collected following participant discontinuation from the study except for concomitant medication use associated with study drug-related adverse events or adverse events that lead to discontinuation from study.

7.10.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related AE):

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than SAR444881
- Radiation therapy

Note: During Part 1, radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. During Part 2, palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Radiotherapy for tumor control is not permitted during the study; however,

radiotherapy for symptom management is allowed, after discussion with and approval by the Sponsor. In addition, if the only evaluable lesions are to be irradiated, the patient should discontinue study treatment.

- Live or live attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Note: Killed vaccines are allowed.

Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

- Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.
- Immunosuppressive doses of systemic corticosteroids (except as stated in [Section 7.11](#))

No concomitant medications (prescription, over-the-counter or herbal) are to be administered during the study unless they are prescribed for treatment of specific clinical events.

7.10.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses XXXX mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

For participants who need to undergo elective surgery (not tumor-related) during the study, it is recommended to hold study drug for at least 2 weeks before and 2 weeks after surgery, or until the participant recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to $\leq$ Grade 1 or baseline and participants must meet relevant eligibility criteria as determined by the Medical Monitor in discussion with the Investigator. The Medical Monitor must be consulted prior to re-initiating treatment in a participant with a dosing interruption lasting > 3 weeks after the last dose.

7.10.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (e.g. allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (i.e. estimated glomerular filtration rate < 30 mL/min/1.73 m²) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standards set by the local Ethics Committee.

7.11 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal

systemic absorption)

- Adrenal replacement steroid doses [REDACTED] mg daily prednisone equivalent
- Thyroid hormone replacement
- A brief [REDACTED] course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen)
- Bone metastases medications (e.g. bisphosphonates, RANKL inhibitors)
- Topical and systemic prophylaxis treatment for cetuximab-related dermatologic toxicity (e.g. oral tetracyclines and topical corticosteroids)

7.12 Treatment After the End of the Study

At the end of the study, Sanofi will not continue to provide Sanofi-supplied study treatment to participants/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

Sanofi reserves the right to terminate access to Sanofi-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of SAR444881 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain the medication from a government sponsored or private health program. In all cases, Sanofi will follow local Health Authorities regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Study treatment is defined as SAR444881, SAR444881 in combination with pembrolizumab, or SAR444881 in combination with cetuximab. Participants MUST discontinue SAR444881 if receiving monotherapy and both SAR444881 and pembrolizumab/cetuximab if receiving combination therapy (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified safety follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator or the Medical Monitor, indicates that continued participation in the study is not in the best interest of the participant.
- Documented disease progression as defined by RECIST v1.1 ([Appendix 7](#)) unless the participant meets criteria for treatment beyond progression ([Section 5.1.4](#)).
- Clinical deterioration while receiving active study therapy that, in the opinion of the Investigator or the Medical Monitor, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in [Section 9.1](#) will require permanent discontinuation.
- Inability to comply with the protocol.
- New anti-cancer therapy is started.

- Termination of the study by Sanofi.
 - Part 1: exceeding the DLT threshold may terminate specific dose cohorts during dose escalation.
 - Part 2: the use of a 2-stage design allows for possible termination of enrollment into an optimization/expansion cohort based on anti-tumor activity evaluation of Stage I participants.
 - Additionally, Sanofi continuously evaluates the benefit/risk of the program and may choose to terminate the development of SAR444881 for reasons including, but not limited to, safety and efficacy.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g. infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and Sanofi approval is required).
- Individual participants with confirmed Complete Response (CR) will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the investigator and the Medical Monitor in settings where benefit/risk justifies discontinuation of study therapy.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
 - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
 - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor.
 - Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 2 weeks, or more frequently if clinically indicated, during such dosing delays.
- Completion of 35 cycles for patients in Cohort A1 and B1 or 2 years of treatment for Cohorts C1, D1, and E1.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the Medical Monitor must occur. In combination cohorts, if there is toxicity requiring discontinuation and the toxicity is considered related to one study drug while clinical benefit has been observed, treatment with the study drug to which the toxicity is attributed must be discontinued, but may be resumed for the other study drug, but only after discussion and agreement with the Medical Monitor. In case of immune-mediated AEs, when signs or symptoms have developed after administration of SAR444881 and pembrolizumab, if discontinuation criteria are met, both study drugs should be discontinued. The consideration to continue study therapy will be made on a case-by-case basis after considering the overall benefit/risk profile.

In the case of pregnancy, the investigator must immediately and within 24 hours of awareness of the pregnancy, notify the Medical Monitor of this event. The study treatment will be permanently discontinued in an appropriate manner. Refer to [Section 10.2.4 Pregnancy](#).

All participants who discontinue study treatment should comply with protocol specified safety follow-up procedures as outlined in [Section 2](#). The only exception to this requirement is when a

participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (e.g. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

The reason for study treatment discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- 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.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 TOXICITY AND MANAGEMENT

9.1 Dose-Limiting Toxicities (DLTs)

For the purpose of guiding decisions regarding dose escalation in Part 1, DLTs will be defined based

A DLT will be defined as any drug-related AE during the 28 days starting with Day 1 of Cycle 1 (at any dose) that meets one or more of the criteria below:

- [illegible]

In addition, for all cycles, the SRC may identify any event that is severe, life-threatening, or results in impairment of daily functions as a DLT, in which case, the next lower dose may be considered by the SRC as defining the MTD.

The Sponsor or designee should be notified of all adverse events that meet DLT criteria within 24 hours.

Immuno-oncology agents, such as SAR444881 and pembrolizumab, are associated with immune-mediated AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of these AEs may mitigate severe toxicity. See [Appendix 6](#) for recommended management algorithms of immune-mediated AEs.

Consulting the Medical Monitor prior to withholding SAR444881, pembrolizumab or cetuximab doses is strongly encouraged.

Participants who require delay of SAR444881, pembrolizumab, cetuximab, carboplatin, or pemetrexed should be re-evaluated weekly or more frequently if clinically indicated and those not meeting guidelines for permanent discontinuation will be permitted to resume dosing when re-

treatment criteria are met ([Section 9.2.3](#)). Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose.

The end of cycle tumor assessments, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), will continue on the schedule defined in [Section 2](#) Schedule of Activities relative to the participant's first dose, regardless of any treatment delay incurred.

9.2.1 Withholding SAR444881 Doses

Delaying SAR444881 administration in participants receiving monotherapy or administration of both SAR444881 in participants receiving combination therapy should be considered for the following:

[REDACTED]

In participants administered SAR444881 in combination with cetuximab, cetuximab treatment may continue if observed AEs are considered by the investigator to be SAR444881 -specific (e.g. imAEs). See [Appendix 6](#) for recommended management algorithms of immune-mediated AEs. Dose modification for adverse events related to pembrolizumab should only be managed according to the framework shown in [Table 9.3-1](#).

9.2.2 Withholding Cetuximab Doses

Delaying cetuximab administration should be considered for the following:

- Grade 3 or 4 dermatologic toxicity (e.g., acneiform rash, mucocutaneous disease)
- Acute onset or worsening of pulmonary symptoms
- Signs and symptoms suggestive of ulcerative keratitis
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

In participants administered SAR444881 in combination with cetuximab, SAR444881 treatment may continue if observed AEs are considered by the investigator to be cetuximab-specific (e.g. expected skin toxicity). See [Section 9.5](#) for recommended management of cetuximab toxicity.

Finally, the following criteria for discontinuation will apply:

- Patients with Grade 4 hypertension must not receive further treatment with cetuximab.
- Patients with Grade 3 or 4 infusion reaction must not receive further treatment with cetuximab.

9.2.3 Withholding Carboplatin and Pemetrexed Doses

Refer to [Section 7.5.1](#).

9.2.4 **Criteria to Resume Treatment**

Participants may resume treatment with study treatment when the drug-related AE(s) resolve to [REDACTED] value, with the following exceptions:

- Participants may resume treatment in the presence of [REDACTED] fatigue
- SAR444881-related skin AE: Participants who have not experienced a [REDACTED] drug-related skin AE may resume treatment in the presence of [REDACTED] skin toxicity
- Pembrolizumab-related skin AE: Participants who have not experienced a [REDACTED] drug-related skin AE may resume treatment in the presence of [REDACTED] skin toxicity
- Cetuximab-related skin AE: Participants may resume treatment in the presence of [REDACTED] skin toxicity
- For participants with [REDACTED] AST, ALT and/or Total Bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete
- Drug-related pulmonary toxicity must have resolved to [REDACTED] before treatment is resumed. Participants with persistent SAR444881 or pembrolizumab-related [REDACTED] pneumonitis after completion of a steroid taper over at least [REDACTED] may be eligible for retreatment if discussed with and approved by the Medical Monitor
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

9.3 **Management Algorithms for Immuno-Oncology Agents**

Immuno-oncology (I-O) agents are associated with immune-mediated AEs (imAEs) that can differ in severity and duration from AEs caused by other therapeutic classes. SAR444881 and pembrolizumab are considered I-O agents in this protocol.

The primary facets of imAE management include recognition and grading of toxicity, immunosuppression, and individualized modification to immune checkpoint administration [194]. Early recognition of symptoms and prompt intervention are key goals for the management of imAEs associated with I-O agents and may mitigate severe toxicity. Significant imAEs often necessitate holding immunotherapy, with permanent discontinuation of the class of agent associated with the toxicity in the setting of certain severe imAEs.

Management algorithms for potential SAR444881 imAEs have been developed, based on algorithms of approved I-O drugs [4, 220], to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies

- Skin
- Neurologic

The clinical nature of AEs noted with SAR444881 will determine the role of the algorithms for use in toxicities related to its use in this study. The algorithms recommended for the management of imAEs in this protocol are in [Appendix 6](#) and in the SAR444881 Investigator's Brochure. Discussions with the Medical Monitor on how to apply these algorithms are strongly encouraged. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These imAEs 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. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most imAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected imAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of imAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for imAEs associated with pembrolizumab are provided in [Table 9.3-1](#).

Table 9.3-1 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444881

General instructions:

1. Severe and life-threatening imAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the imAEs are not controlled by corticosteroids.
2. Pembrolizumab and SAR444881 must be permanently discontinued if the imAE does not resolve or the corticosteroid dose is not ██████████ mg/day within ██████████ weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the imAE is ██████████ and continue at least ██████████ weeks.
4. If pembrolizumab and SAR444881 have been withheld, pembrolizumab and SAR444881 may resume after the imAE decreased to ██████████ after corticosteroid taper.

imAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444881	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	██████████	Withhold	Administer corticosteroids (initial dose of ██████████ mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of pneumonitis.
	Recurrent ██████████ ██████████	Permanently discontinue	Add prophylactic antibiotics for opportunistic infections.	Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
Diarrhea/Colitis	██████████	Withhold	Administer corticosteroids (initial dose of ██████████ mg/kg	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain,

imAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444881	Corticosteroid and/or other therapies	Monitoring and follow-up
	Recurrent [REDACTED] [REDACTED]	Permanently discontinue	prednisone or equivalent) followed by taper.	blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with $\geq$ [REDACTED] diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST or ALT elevation or Increased Bilirubin/hepatitis	[REDACTED]	Withhold	Administer corticosteroids (initial dose of [REDACTED] mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider [REDACTED] or more frequently until liver enzyme value returned to baseline or is stable).
	[REDACTED]	Permanently discontinue	Administer corticosteroids (initial dose of [REDACTED] mg/kg prednisone or equivalent) followed by taper.	
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia including diabetic ketoacidosis	New onset T1DM or [REDACTED] 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	[REDACTED]	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	[REDACTED]	Withhold or permanently discontinue ^d		
Hyperthyroidism	[REDACTED]	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	[REDACTED]	Withhold or permanently discontinue ^d		
Hypothyroidism	[REDACTED]	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.

imAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444881	Corticosteroid and/or other therapies	Monitoring and follow-up
Nephritis: grading according to increased creatinine or acute kidney injury	██████ ██████	Withhold Permanently discontinue	Administer corticosteroids (prednisone █████ mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Neurological Toxicities	██████ ██████	Withhold Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously ████████ ██████	Withhold Permanently discontinue	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
All Other imAEs	Persistent ████████ ██████ Recurrent ████████ ██████	Withhold Withhold or discontinue based on the event ^e Permanently discontinue	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.

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-imAE will be managed as appropriate, following clinical practice recommendations.

██
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^d The decision to withhold or permanently discontinue pembrolizumab and SAR444881 is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab and SAR444881 may be resumed.

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

9.4 Management of Drug-Related Infusion Reactions and Cytokine Release Syndrome

Infusion reactions have been reported for immuno-oncology and monoclonal antibody drugs. Cetuximab can cause serious and fatal infusion reactions. Pembrolizumab has also been reported to

cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis. If such a reaction were to occur with SAR444881, cetuximab or chemotherapy infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, wheezing, flushing, loss of consciousness, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor and reported as an SAE if it meets the criteria.

Refer to [Table 9.4.1-1](#) for treatment recommendations for pembrolizumab-related infusion related reactions. Treatment recommendations are provided below for all other study drugs. Recommendations may be modified based on local treatment standards and guidelines and cetuximab Prescribing Information, as appropriate:

For **Grade 1** symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at the bedside and monitor the participant until recovery from symptoms. For cetuximab infusions reduce the rate of infusion by 50%.
- The following prophylactic premedications are recommended for future infusions: Diphenhydramine [REDACTED] mg (or equivalent) and/or acetaminophen/paracetamol [REDACTED] mg at least 30 minutes before subsequent infusions.

For **Grade 2** symptoms (moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine [REDACTED] mg IV (or equivalent) and/or acetaminophen/paracetamol [REDACTED] mg; remain at the bedside and monitor the participant until resolution of symptoms.
- Corticosteroid and/or bronchodilator therapy may also be administered as appropriate.
- If the infusion is interrupted, then restart the infusion at [REDACTED] of the original infusion rate when symptoms resolve; if no further complications ensue after [REDACTED] minutes, the rate may be increased to [REDACTED] of the original infusion rate. Monitor participant closely.
- If symptoms recur after restarting the infusion, then no further study drug(s) will be administered at that visit. Administer diphenhydramine [REDACTED] mg IV, remain at the bedside, and monitor the participant until resolution of symptoms.
- For future infusions, the following prophylactic premedications are recommended approximately [REDACTED] minutes prior to subsequent SAR444881 administrations: Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol [REDACTED] mg should be administered at least [REDACTED] minutes before the infusion. If necessary, [REDACTED] may be used.

For **Grade 3 or Grade 4** symptoms: (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine [REDACTED] mg of a [REDACTED] solution for subcutaneous administration or [REDACTED] mg of a [REDACTED] solution injected slowly for IV administration, and/or diphenhydramine [REDACTED] mg IV with [REDACTED] mg IV

(or equivalent), as needed.

- Remain at the bedside and monitor the participant until recovery of the symptoms. The participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
- For all drugs other than cetuximab, study drug(s) will be permanently discontinued except for a Grade 1 infusion reaction that returns to Grade 1 in less than 24 hours. In such cases prophylactic premedications are recommended (see Grade 2 treatment recommendations above).
- Cetuximab will be permanently discontinued for either a Grade 3 or Grade 4 infusion reaction.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

If during the first cetuximab infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have pre-formed IgE antibodies before a subsequent infusion is given. If a participant experiences a mild or moderate cetuximab infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Premedication in participants treated with SAR444881 in combination with pembrolizumab should be administered prior to the first study drug planned to be infused.

All participants treated with SAR444881 in combination with cetuximab will be premedicated with a [REDACTED]. Premedication should be administered prior to the cetuximab infusion. If [REDACTED] are planned to be added they should be administered prior to the cetuximab infusion along with the [REDACTED]. Investigators should consider the duration of infusion and the time between cetuximab and SAR444881 administrations; another dose of [REDACTED] may be needed prior to SAR444881 administration in the event of a prolonged time difference between the two study drugs infusions.

Dependent on incidence and severity of observed infusion related reactions, precautions applicable to all study participants, e.g. mandatory premedication, will be discussed by the Sponsor and the SRC.

Management of Cytokine Release Syndrome

Cytokine release syndrome (CRS) is not an anticipated risk for SAR444881 at this stage, however IRR may be anaphylactic or anaphylactoid in nature and may represent CRS. Symptoms may occur during the first infusion or up to several hours after the infusion, or with subsequent infusions, typically less commonly associated with bronchospasm or urticaria than IgE mediated reactions. Common symptoms include fever, pyrexia, chills, hypotension and hypoxia. To assess and record the severity of CRS in individual participants, the ASTCT Consensus Guidelines 2019 [221] will be used (Table 9.4-1).

Table 9.4-1: Grading system and management strategy for CRS

Grade	CRS parameter	Intervention
Grade 1	Fever ^a	- Vigilant supportive care. - Assess and treat infection if present. - Fluid resuscitation. - Provide antipyretics and analgesics, if needed. - No dose modification required.
Grade 2	Fever ^a with Hypotension not requiring vasopressor and/or ^b Hypoxia requiring low-flow nasal cannula ^c or blow-by.	- Vigilant supportive care (Assess for infection; treat febrile neutropenia if present, monitor fluid balance, - antipyretics/analgesics as needed); monitor cardiac and other organ functions closely; symptomatic - management of organ toxicities participants with comorbidities, older age, those who require oxygen or participants in whom symptoms (eg, high grade fever) do not respond to antipyretics within 72 hours: Consider tocilizumab or alternative therapies per site practice in CRS management and/or corticosteroids - Pause infusion/treatment, may resume treatment when clinical symptoms resolve to baseline or Grade 1 - No dose modification required. Consider slowing infusion
Grade 3	Fever ^a with Hypotension requiring a vasopressor with or without vasopressin and/or ^b Hypoxia requiring high-flow nasal cannula, ^c facemask, nonrebreather mask, or Venturi mask	- Vigilant supportive care as per Grade 2; tocilizumab or alternative therapies per site practice in CRS management and/or corticosteroids; vasopressor support for fluid refractory hypotension and intensive care unit (ICU) care as needed; supplemental oxygen as needed. - Pause infusion/treatment, may resume treatment when clinical symptoms resolve to baseline or Grade 1 - If with initial dose, re-treat with initial dose - If with transitional dose, re-treat with dose that is not higher than transitional dose - If with full dose, reduce by at least 50% and then escalate as tolerated - In case of recurrent Grade 3 CRS, permanently discontinue all study drug treatments that were associated with CRS.
Grade 4	Fever ^a with Hypotension requiring multiple vasopressors (excluding vasopressin) and/or ^b Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	- Vigilant supportive care as for Grade 2, but with the addition of corticosteroids and/or anti-IL-6 therapy. - Permanently discontinue all study drug treatment associated with CRS.
Grade 5	Death	

Grade	CRS parameter	Intervention
BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; ICU=intensive care unit; IL-6=interleukin 6.		
a	Fever is defined as $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent 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/min. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.	

9.4.1 ***Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab***

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 9.4.1-1](#).

Table 9.4.1-1 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 (e.g., 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 (e.g. 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 1.5h ($\pm$ 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Table 9.4.1-1 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at https://ctep.cancer.gov .		

9.5 Management of Cetuximab Dermatologic and Pulmonary Toxicity and Electrolyte Abnormalities

Dermatologic Toxicity

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed in patients who received cetuximab.

Participants receiving cetuximab should be monitored for dermatologic toxicities and infectious

sequelae. Participants should be instructed to limit sun exposure during cetuximab therapy. Prophylactic use of oral tetracyclines, topical corticosteroids and moisturizers should be considered for prevention of dermatological toxicity. Withhold, reduce dose, or permanently discontinue cetuximab based on severity of acneiform rash or mucocutaneous disease in accordance with the instructions in the cetuximab Prescribing Information:

- 1st occurrence of dermatologic toxicity; Grade 3 or 4: Interrupt cetuximab therapy; treatment may only be resumed if the reaction has resolved to grade 2; if condition improves, continue at ■■■ mg/m².
- 2nd occurrence of dermatologic toxicity; Grade 3 or 4: Interrupt cetuximab therapy; treatment may only be resumed if the reaction has resolved to Grade 2; if condition improves, continue at ■■■ mg/m².
- 3rd occurrence of dermatologic toxicity; Grade 3 or 4: Interrupt cetuximab therapy; treatment may only be resumed if the reaction has resolved to Grade 2; if condition improves, continue at ■■■ mg/m².
- 4th occurrence of Grade 3 or 4 dermatologic toxicity: Discontinue cetuximab.

Pulmonary Toxicity

Cetuximab can cause interstitial lung disease. Monitor participants for signs and symptoms of pulmonary toxicity. In case of acute onset or worsening pulmonary symptoms withhold or permanently discontinue cetuximab in accordance with the instructions in the cetuximab Prescribing Information:

- Interrupt cetuximab therapy; if condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease is confirmed, discontinue cetuximab.

Electrolyte Abnormalities

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of cetuximab. In addition, hypokalemia and hypocalcemia may also occur. Serum electrolyte levels will be routinely assessed during the study. Electrolyte repletion is recommended, as appropriate.

10 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities ([Section 2](#)).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Medical Monitor or Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before start of study treatment. 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 (e.g. blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (e.g. suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

10.1 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of SAR444881 as a single agent and in combination with pembrolizumab, cetuximab, pemetrexed, and/or carboplatin will be based on tumor measurements, using RECIST v1.1 as outlined in [Appendix 7](#).

10.1.1 Imaging Assessment for the Study

Screening and on study images should be acquired as outlined in the Schedule of Activities ([Section 2](#)) and continue until withdrawal of consent, disease progression, or initiation of another systemic anti-cancer treatment. Tumor assessments at other timepoints may be performed if clinically indicated. Assessments for all participants should continue as per protocol even if dosing is delayed or discontinued.

Assessment of computed tomography (CT) and magnetic resonance imaging (MRI) scans as tumor assessments will be performed at the study sites during the whole study. If the Sponsor decides, independent central read for CT or MRI scans could be considered in this study, both prospectively and retrospectively.

10.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, CT/MRI of abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST v1.1 criteria.

Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast

CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for MRI (e.g. incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a PET-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST v1.1 measurements. However, if a 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 v1.1 measurements. 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.

Bone scan or PET scan is not adequate for assessment of RECIST v1.1 response in target lesions. In select circumstances where such modalities are the sole modality used to assess certain non- target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

For head and neck cancer participants: CT/MRI of the neck should also be performed as outlined in the Schedule of Activities ([Section 2](#)).

Bone scans may be collected per local standards, as clinically indicated.

10.1.1.2 Imaging and Clinical Assessment

Tumor assessments, as defined in the Schedule of Activities ([Section 2](#)), should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator using RECIST v1.1 criteria (See [Appendix 7](#) for specifics of RECIST v1.1 criteria to be utilized in this study). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks (28 days) after initial response. A Best Overall Response (BOR) of stable disease (SD) requires a minimum of 49 days on study (from date of first dose to the date of the first imaging assessment).

10.1.2

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

10.2 Adverse Events

The definitions of an adverse event (AE) and a serious adverse event (SAE) can be found in [Appendix 3](#).

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 designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on adverse events.

The Investigator is responsible for ensuring that all adverse events are recorded on the CRF and reported to the Sponsor in accordance with instructions provided. For each adverse event recorded on the CRF, the Investigator will make an assessment of seriousness, severity, and causality (see [Appendix 3](#) for additional details).

As far as possible, each adverse event should also be evaluated to determine: its duration (start and end date), action taken with respect to study treatment, whether medication or therapy was given, and outcome.

A diagnosis (if known) should be recorded on the CRF rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the CRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis,

with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis. Investigators should use correct medical terminology/concepts when recording adverse events on the CRF and avoid colloquialisms and abbreviations.

In general, adverse events that occur secondary to other events (e.g. cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events that occur secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. All adverse events should be recorded separately on the CRF if it is unclear as to whether the events are associated.

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the CRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the CRF should be updated to reflect this. A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the CRF.

Immune-mediated adverse events (imAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g. infection or tumor progression) have been ruled out. imAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Every adverse event should be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's CRF.

Instructions on SAE reporting are specified in [Appendix 3](#).

10.2.1 Time Period and Frequency for Collecting AE and SAE Information

After informed consent has been obtained but prior to initiation of any study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g. serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported. After initiation of study drug(s), all adverse events, regardless of relationship to the study drug(s), should be collected continuously during the treatment period and for a minimum of [REDACTED] days (see [Section 10.2.2](#)) following discontinuation of SAR444881, pembrolizumab, cetuximab, carboplatin, or pemetrexed.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, or any non-serious AE of special interest at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in [Appendix 3](#).

10.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning,

examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

10.2.2.1 Part 1 (Dose Escalation)

- Nonserious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see [Appendix 3](#)).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.
- All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in [Section 8.3](#)).

Further information on follow-up procedures is given in [Appendix 3](#).

10.2.2.2 Part 2 (Dose Optimization/Expansion)

- All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment /allocation must be reported by the investigator if the participant is receiving run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
- All AEs or ECIs (Events of Clinical Interest) from the time of treatment/ allocation through ■ days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment/ allocation through ■ days following cessation of study treatment, or ■ days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through ■ days following cessation of study treatment, or ■ days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

10.2.3 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met. SAEs, whether related or not related to study treatment must be reported to Sanofi (or designee) within 24 hours of awareness of the event.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.
- An Investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g. summary or listing of SAEs) from the Sponsor will file it along with the

Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

10.2.4 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study treatment exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the Medical Monitor of this event. Any female patient receiving cetuximab who become pregnant must be advised of the potential risk to a fetus (see USPI section 8.1). In addition, the Investigator must complete and forward a Pregnancy Surveillance Form to Sanofi designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Appendix 3](#).

If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed [REDACTED]

[REDACTED] following approvals of participant/Sponsor/IRB/EC, as applicable.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

10.2.5 Laboratory Test Result Abnormalities

Not every laboratory abnormality qualifies as an adverse event. The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g. anemia versus low hemoglobin value).

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g. "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event (e.g. "hyperkalemia").

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the CRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

10.2.6 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential drug-induced liver injury (DILI) have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see [Appendix 3](#) for reporting details).

Potential drug induced liver injury is defined as:

1. Aminotransaminases (ALT or AST) elevation $> 3\times$ upper limit of normal (ULN) ($> 2\times$ baseline AND $> 3\times$ ULN for participants with baseline elevation)
AND
2. Total bilirubin $> 2\times$ ULN ($> 2\times$ baseline AND $> 2\times$ ULN for participants with baseline elevation) without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND
3. No other immediately apparent possible causes of aminotransaminases elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

The key responsibilities for investigators during DILI assessment include (1) early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities and (2) notification of Sanofi designee of DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, Sanofi is responsible for (1) timely evaluation and triaging of DILI cases, (2) expedited reporting of DILI cases, and (3) expanded review of DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets DILI criteria. They are expected to promptly notify Sanofi designee of all DILI cases. DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a Hepatic Laboratory Panel (ALT, AST, total bilirubin, and ALP). Any participant with an abnormal Hepatic Laboratory Panel that meets DILI criteria is a candidate for study treatment discontinuation. Any confirmed DILI events must be reported (along with a description of the clinical findings) as an

SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, non-exhaustively and by way of example only, the following: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases, autoimmune diseases (such as primary biliary cholangitis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

10.2.7 Immune-mediated Adverse Events

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune mediated component for which non-inflammatory etiologies (e.g. infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF. See [Section 3.2.8](#) for SAR444881 and pembrolizumab anticipated risks and [Appendix 6](#) for recommended management algorithms of immune-mediated AEs.

10.2.8 Abnormal Vital Signs Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the Investigator's responsibility to review all vital signs findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event. If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g. high blood pressure), only the diagnosis (i.e. hypertension) should be recorded on the CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the CRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

10.2.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded as part of the participant's medical history. A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable

descriptors (e.g. “more frequent headaches”).

10.2.10 Other Safety Considerations

- Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.
- To ensure the safety of study participants, access to the study’s Medical Monitor is available 24 hours a day, 7 days a week.

10.3 Overdose, Medication Errors, Misuses or Abuses of Medicinal Product

For the study, overdose is defined as follows:

- IMP overdose:
 - Any administration of SAR444881, cetuximab, carboplatin, or pemetrexed at least 30% above the intended dose at each administration
 - For pembrolizumab, an overdose is defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
- AxMP overdose is defined as at least twice the intended dose within the therapeutic interval.

Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see [Appendix 3](#)).

In the event of an overdose the investigator should:

- 1) Contact the Medical Monitor immediately
- 2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically
- 3) Obtain a serum sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)
- 4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

All reports of overdose, medication error, misuse or abuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor’s representative following standard processes. The Investigator will assess whether or not the overdose, medication error, misuse or abuse event has to be reported together with an AE or SAE.

A medication error is an unintended failure in the drug treatment process (i.e., mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, i.e., not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, i.e., intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, “getting high”(euphoria).

This includes situations in which a participant was involved or not (e.g., even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not. Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

10.4 Adverse Events of Special Interest (AESI; Part 2 only)

Selected non-serious and serious adverse events are also known as Adverse Events of Special Interest (AESI) and must be reported to the Sponsor within 24 hours of awareness.

AESIs for this trial include:

1. an overdose of Sponsor's product, as defined in [Section 10.3](#) – Overdose, Medication Errors, Misuses or Abuses of Medicinal Product, that is not associated with clinical symptoms or abnormal laboratory results.
2. 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 Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

10.5 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities ([Section 2](#)).

10.5.1 Electrocardiograms (ECGs) and Left Ventricular Ejection Fraction (LVEF)

██████████ will be performed at the timepoints as specified in the Schedule of Activities ([Section 2](#)) and read locally. ██████████ will be performed at screening then, as clinically indicated in Part 2 only. To minimize variability, the participant should be relaxed and should be in a resting position at least 5 minutes before ██████████. Environmental distractions (e.g. television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. The ECG should be performed ██████████

██████████ ECGs may be performed after IV-line insertions or blood draws once a

reasonable time has passed and the participant is relaxed. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement that may contribute to the abnormality in ECG results.

██████████ will be done in Part 2 by ██████████, and any repeated assessment should be done with the same technology used at screening.

For participants in Part 1, ██████████ will be collected along time matched PK collections to evaluate the potential cardiac effect of SAR444881 as a single agent and in combination with pembrolizumab, cetuximab, carboplatin, or pemetrexed (e.g. QTc prolongation). See [Table 10.5-1](#), [Table 10.5-2](#), and [Table 10.5-3](#) for schedule of ██████████. For participants in Part 2, pre-dose ██████████ will be performed at the timepoints described in [Table 10.5-4](#) and [Table 10.5-5](#).

For all participants, additional ██████████ should be performed in case of abnormalities and if clinical symptoms occur.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ██████████ and the review will be documented in the CRF. ECGs will be available for comparison with previous and subsequent ECGs by the Investigator. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

The following will be recorded in the CRF for ECG tracings:

- Heart rate (bpm)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QT interval corrected according to the method of Fridericia (QTcF; msec)
- Overall ECG interpretation

For any clinically significant abnormal results, the Investigator must contact the Medical Monitor to discuss continued participation of the participant in the study (e.g. ischemic ECG changes, wave/interval changes, or arrhythmia).

Only clinically significant abnormalities will be recorded in the AE CRF page. Clinically significant abnormalities at Screening should be recorded on the relevant medical history/current medical conditions CRF page.

10.5.2 Physical Examinations

A Physical Examination (including vital signs and examination of general appearance, skin [including assessment of infusion site], head, eyes, ears, nose, throat, neck, joints, lungs, heart, abdomen [including liver and spleen], lymph nodes, extremities, cardiovascular system, musculoskeletal system, and neurological system) or Target Physical Examination (targeted to signs and symptoms) will be performed as indicated in the Schedule of Activities ([Section 2](#)). All abnormal findings at baseline will be documented and recorded in the source documents and the CRF. Any physical examination finding that is judged by the Investigator as a clinically significant change

(worsening) compared to a baseline value will be considered an adverse event and will be recorded and monitored as described in [Section 10.2](#).

10.5.3 Vital Signs

Vital signs measurements include:

- Temperature (°C)
- Respiratory Rate
- Pulse (beat/minute)
- Resting systolic and diastolic blood pressure (mmHg)

Before pulse and blood pressure are measured, the participant should be in a sitting position and resting for at least 5 minutes.

Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded and monitored as described in [Section 10.2](#).

Vital Signs Monitoring During SAR444881 Infusions

Sub-Parts 1A/1C and Part 2: At SAR444881 administration visits during Cycle 1, vital signs will be measured pre-infusion, every ■ minutes until the end of infusion, and thereafter, every ■ minutes until the infusion line is removed. In Cycles ■, vital signs will be measured pre-infusion, every ■ minutes during the infusion and every ■ minutes post-infusion until the infusion line is removed. From Cycle ■ onwards, vital signs at administration visits will only be obtained pre-infusion.

Sub-Part 1B: At SAR444881 administration visits during Cycles ■, vital signs will be measured pre-infusion, every ■ minutes until the end of infusion, and thereafter, every ■ minutes until the infusion line is removed. In Cycles ■, vital signs will be measured pre-infusion, every ■ minutes during the infusion and every ■ minutes post-infusion until the infusion line is removed. From Cycle ■ onwards, vital signs at administration visits will ■.

For all study participants, after the end of the first two SAR444881 infusions, the ■ should remain in place for ■. If no infusion-related symptoms occur during this time, the infusion line may be removed. For subsequent infusions and if no drug-related infusion reaction has been reported, the ■ should remain in place for ■ minutes after the end of infusion and if no adverse events occur during the ■ minutes, the ■ may be removed.

Vital Signs Monitoring During Pembrolizumab, Pemetrexed, and Carboplatin Infusions

In cycles 1 through 4, vital signs will be measured pre-infusion and at the end of the pembrolizumab, pemetrexed, and carboplatin infusions. For pembrolizumab and pemetrexed, from Cycle 5 onwards, vital signs will only be obtained pre-infusion.

Vital Signs Monitoring During Cetuximab Infusions

In cycle 1, vital signs will be measured pre-infusion, every 30 minutes during the cetuximab infusion and every 30 minutes post-infusion. In Cycles 2 and 3, vital signs will be measured pre-infusion, every 60 minutes during the infusion and every 30 minutes post-infusion. From Cycle 4 onwards, vital signs will be obtained pre-infusion and at the end of the infusion.

Vital signs should be obtained ± 5 minutes from the scheduled times noted above. The frequency of vital signs measurements necessary to monitor an adverse event will be determined by the Investigator.

10.5.4 Tumor Tissue Specimens

Tumor biopsy specimens will be obtained in the study to examine immune infiltrates and expression of select tumor markers.

Tissue specimens in the form of fresh tissue, a paraffin-embedded block or unstained slides will be submitted for central immunohistochemistry assessment. Tumor biopsy samples should be excisional, incisional, or core needle as fine needle aspirates and other cytology specimens are insufficient for downstream biomarker analyses. Bone lesion biopsies are unacceptable for submission since the decalcification process is not compatible with several of the planned biomarker analyses.

Tumor samples may be assessed for the expression of immune related genes, RNAs and/or proteins, as well as for the presence of immune cell populations using a variety of methodologies including but not limited to immunohistochemistry, qualitative real-time PCR, flow cytometry (FACS), and gene expression profile. Other methods of tumor biomarker expression are being evaluated.

Both the screening and on-treatment tumor biopsies should be preferentially collected from the same site, if feasible. At the time of progression, biopsies should be performed using a progressive lesion or a new lesion, if feasible. Screening and on-treatment biopsies are mandated in participants of Sub-Part [REDACTED] dose level cohorts of [REDACTED] mg/kg and above and all Sub-Parts 1 [REDACTED]/1 [REDACTED] and collected in Part 2 participants as per inclusion criteria. [REDACTED]

[REDACTED] and must be collected prior to the scan. Additional participants may be added if adequate paired pre-treatment and on-treatment biopsy specimens are not obtained.

A biopsy sample of participants that have disease progression on study drug for understanding mechanisms of resistance to therapy is optional. All participants in Part 1 will be asked for their consent for an optional end of treatment biopsy. If upon disease progression a participant is to be imminently (within 4 weeks) enrolled in a subsequent clinical trial that requires a tumor biopsy, then the new trial enrollment criteria supersede the required post-progression tumor biopsy.

The Medical Monitor should be notified if on-treatment biopsy may pose unacceptable clinical risk or if tumor at the time of on-treatment biopsy is not accessible for sampling. Institutional guidelines for the safe performance of biopsies should be followed.

The screening, on-treatment, and upon progression biopsies will follow the same guidance methodology for sample collections, processing, and submission provided in the Laboratory Manual.

10.5.5 Performance Status Assessment

An assessment of performance status will be performed using the ECOG performance status scale described in [Table 10.4.4-1](#).

Table 10.4.4-1 ECOG Performance Status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Refer to Schedule of Activities ([Section 2](#)) for timing of assessments for performance status.

10.5.6 Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be performed by a local laboratory per the Schedule of Activities ([Section 2](#)). More frequent assessments may be performed at the Investigator's discretion if medically indicated. If convenient for participants, samples may be drawn and tested at the site's laboratory up to 48 hours before study drug(s) administration. The laboratory tests that will be performed for study participants are shown in [Table 10.4.5-1](#).

The Investigator or a qualified Sub-Investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (e.g. is associated with signs and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in [Section 10.2](#). Investigators should document their review of each laboratory safety report.

Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either on the laboratory pages of the CRF or by another mechanism as agreed upon between the Investigator and Sanofi (e.g. provided electronically). If the units of a test result differ from those appearing in the CRF, the recorded laboratory values must specify the correct units.

Table 10.4.5-1: Clinical Laboratory Assessments
Hematology
Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

Chemistry / Liver Function Tests	
Alkaline phosphatase	Creatinine clearance (CL _{cr}) calculated by the Cockcroft-Gault equation (<u>screening only</u>)
Aspartate aminotransferase (AST)	Creatinine kinase/Creatinine phosphokinase
Alanine aminotransferase (ALT)	Glucose
Gamma glutamyl transferase (GGT) (<u>reflex only</u>)	Lactate dehydrogenase (LDH)
Total bilirubin	Lipase
Direct bilirubin (<u>reflex only</u>)	Magnesium
Albumin	Phosphorus
Total Protein	Potassium
Amylase	Sodium
Blood Urea Nitrogen (BUN)	Uric acid
Calcium	Thyroid stimulating hormone
Chloride	Free T3 ¹ and T4 (<u>screening and reflex only</u>)
Creatinine	
Coagulation Profile	
Prothrombin time (PT) or International Normalized Ratio (INR), Partial thromboplastin time (PTT)	
Urinalysis (Dipstick)	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology <i>screening only</i>	
Hepatitis B/C (HBsAg, HCV antibody or HCV RNA)	
HIV-1 and -2 (antibody) as applicable to meet local requirements	
Other Analyses	
Pregnancy test (WOCBP only). Serum or urine test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).	
Follicle stimulating hormone (FSH) screening only required to confirm menopause in women < age 55 who have not undergone hysterectomy	
T3, FT4, TSH and cortisol tests will be performed <u>in Part 2 only</u> every 2 cycles throughout the entire treatment period and at EOT in cohorts receiving pembrolizumab (Part 2, Cohorts A1 and B1)	
Reflex testing	
Direct Bilirubin: to be performed only if total bilirubin is abnormal	
GGT: to be performed only if liver function test is abnormal	
Free T3 ¹ and Free T4: to be performed only if TSH is abnormal (Part 1, and Part 2 Cohorts C1, D1, and E1 only)	

1. Total T3 may alternatively be tested dependent on local standards

10.5.7 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Investigator as per standard medical/clinical judgment.

10.6 Pharmacokinetics

The Pharmacokinetics (PK) of SAR444881 will be assessed in both parts of the study and will be derived from serum concentrations versus time data. Serum concentration data will be tabulated using summary statistics. These data may also be pooled for population PK and ER analysis, which will be presented in a separate report. In addition, model-determined exposures may be used for exposure-response analyses.

The pharmacokinetic parameters to be assessed, if data permit, may include, but are not limited to:

$C_{\max}$	Maximum observed serum concentration
C_{eoi}	Concentration observed at the end of an intravenous (IV) infusion
C_{trough}	Serum concentration observed at the end of the dosing interval or just before treatment administration during repeated dosing
$T_{\max}$	Time of maximum observed serum concentration
$T_{1/2}$	Terminal elimination half-life
$AUC_{(0-T)}$	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
$AUC_{(\text{INF})}$	Area under the serum concentration-time curve from time zero extrapolated to infinite time

Table 10.5-1, Table 10.5-2, Table 10.5-3, Table 10.5-4, and Table 10.5-5 list the sampling schedule to be followed for the assessment of the PK of SAR444881 in Parts 1 and 2. All time points are relative to the start of SAR444881 administration. SAR444881 Pre-dose samples should be taken within 30 minutes before the start of SAR444881 dose administration in single agent cohorts and before the start of pembrolizumab/cetuximab administration in combination cohorts. End-of-infusion samples should be taken just prior to the end of infusion (preferably within 2-5 minutes). On-treatment PK samples are intended to be drawn relative to actual dosing days. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. End and post infusion PK samples (end-of-infusion, 4 hours, and 8 hours timepoints) should not be collected from the same IV access as drug was administered.

Serum samples for pembrolizumab and cetuximab will be collected based on the sampling schedule for Dose Optimization/Expansion Cohorts (Table 10.5-4 and Table 10.5-5). Samples will be stored for potential analysis if further investigations are needed.

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the Laboratory Manual.

10.7 Immunogenicity

Immunogenicity refers to the development of an immune response to SAR444881 and is characterized by antibodies that the participant may develop that react with SAR444881. These may result in more rapid clearance of SAR444881 from the bloodstream or predispose the participant to an infusion reaction if the participant is to be retreated with SAR444881 later.

Serum samples collected at timepoints identified in [Table 10.5-1](#), [Table 10.5-2](#), [Table 10.5-3](#), [Table 10.5-4](#), and [Table 10.5-5](#) will be analyzed by a validated immunoassay for SAR444881 immunogenicity. Additional characterization (i.e. neutralizing antibodies) for any detected anti-drug antibodies (ADA) response to SAR444881 may also be performed using a validated functional cell-based assay. Blood samples for immunogenicity analysis will be collected from all participants at baseline, on-treatment and in the follow up period.

All on-treatment immunogenicity assessment timepoints are intended to align with days on which SAR444881 is administered. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected, but the dose is subsequently delayed, an additional pre-dose sample should not be collected.

Immunogenicity of Pembrolizumab will not be assessed unless further investigations are needed, given the fact that the incidence of anti-drug antibody (including neutralizing antibody) positivity is not comparable across studies and assays, due to several factors, including but not limited to differences in assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Participants with positive treatment-emergent anti-pembrolizumab antibody is approximately 2% (0.5% positive neutralizing antibody) according to US Package Insert, and there was no evidence of an altered PK profile or increased infusion reactions in these participants. In addition, pembrolizumab showed flat exposure-response profile in terms of safety across a dose range of 1 to 10 mg/kg, and it is unlikely for SAR444881 to trigger additional safety concerns of pembrolizumab, due to altered immunogenicity.

Unless further investigations are needed, immunogenicity of Cetuximab will not be assessed given the fact that the incidence of anti-cetuximab binding antibodies in 105 patients with at least one post-baseline blood sample (≥ 4 weeks post first cetuximab administration) was $<5\%$ according to US Package Insert.

An extra aliquot of serum sample will be collected for ADA assessment in [Table 10.5-4](#) and [Table 10.5-5](#), and stored for potential analysis if further investigations are needed for assessment of immunogenicity of Pembrolizumab or Cetuximab.

In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (e.g. if there is insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 10.5-1: Sub-Part 1A (SAR444881 Single Agent Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		ADA Serum Sample	
C1D1	Predose	0:00		X	
	EOI	1:00 ^h			
		4:00 ^f			
		8:00 ^f			
C1D2		24:00 ^g			
C1D8		168:00 ^d			
C1D15	Predose	0:00			
	EOI	1:00 ^h			
C1D22		168:00 ^d			
C2D1	Predose	0:00		X	
	EOI	1:00 ^h			
C2D15	Predose	0:00			
	EOI	1:00 ^h			

Table 10.5-1: Sub-Part 1A (SAR444881 Single Agent Dose Escalation) Pharmacokinetic, Immunogenicity and ECG Sampling Schedule

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		ADA Serum Sample	██████████ ██████
C3D1	Predose	0:00		X	
	EOI	1:00 ^h			
		4:00 ^f			
		8:00 ^f			
C3D15	Predose	0:00			
	EOI	1:00 ^h			
Cycle X Day 1	Predose	0:00		X ^e	
Cycle X Day 15	Predose	0:00			
End of Treatment					
Follow Up 30 Day				X	
Follow Up 60 Day				X	
Follow Up 90 Day				X	

**Table 10.5-2: Sub-Part 1B (SAR444881 in Combination with Pembrolizumab Dose Escalation)
Pharmacokinetic, Immunogenicity and ECG Sampling Schedule**

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		ADA Serum Sample	
C1D1	Predose	Before Pembrolizumab Infusion		X	
	SAR444881 EOI	1:00			
		4:00 ^f			
		8:00 ^f			
C1D2		24:00 ^g			
C1D8		168:00 ^d			
C1D15		336:00 ^d			
C2D1	Predose	Before Pembrolizumab Infusion		X	
	SAR444881 EOI	1:00			
C2D8		168:00 ^d			
C2D15		336:00 ^d			

Pharmacokinetic, Immunogenicity and ECG Sampling Schedule

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)	ADA Serum Sample
C3D1	Predose	Before Pembrolizumab Infusion	X
	SAR444881 EOI	1:00	
		4:00 ^f	
		8:00 ^f	
C3D8		168:00 ^d	
Cycle X Day 1	Predose	Before Pembrolizumab Infusion	X ^e
<i>End of Treatment</i>			
<i>Follow Up 30 Day</i>			X
<i>Follow Up 60 Day</i>			X
<i>Follow Up 90 Day</i>			X

[illegible]

**Table 10.5-3: Sub-Part 1C (SAR444881 in Combination with Cetuximab Dose Escalation)
Pharmacokinetic, Immunogenicity and ECG Sampling Schedule**

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		ADA Serum Sample	
C1D1	Predose	Before Cetuximab Infusion		X	
	SAR444881 EOI	1:00			
		4:00 ^f			
		8:00 ^f			
C1D2		24:00 ^g			
C1D8		168:00 ^d			
C1D15	Predose	Before Cetuximab Infusion			
	SAR444881 EOI	1:00			
C1D22		168:00 ^d			
C2D1	Predose	Before Cetuximab Infusion		X	
	SAR444881 EOI	1:00			
C2D15	Predose	Before Cetuximab Infusion			
	SAR444881 EOI	1:00			

**Table 10.5-3: Sub-Part 1C (SAR444881 in Combination with Cetuximab Dose Escalation)
Pharmacokinetic, Immunogenicity and ECG Sampling Schedule**

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		ADA Serum Sample	
C3D1	Predose	Before Cetuximab Infusion		X	
	SAR444881 EOI	1:00			
		4:00 ^f			
		8:00 ^f			
C3D15	Predose	Before Cetuximab Infusion			
	SAR444881 EOI	1:00			
Cycle X Day 1	Predose	Before Cetuximab Infusion		X ^e	
Cycle X Day 15	Predose	Before Cetuximab Infusion			
<i>End of Treatment</i>					
<i>Follow Up 30 Day</i>				X	
<i>Follow Up 60 Day</i>				X	
<i>Follow Up 90 Day</i>				X	

[illegible]

Table 10.5-4: Part 2 (SAR444881 Dose Optimization Cohort C1 and E1 and Dose Expansion Cohort D1) Pharmacokinetic, Immunogenicity and ECG Sampling

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		Cetuximab PK Serum Sample (C1, E1)	ADA Serum Sample	
C1D1	Predose	0:00 ^h		X	X	
	EOI	1:00		X ^d		
C1D2		24:00 ^e				
C1D8	168	168:00 ^f				
C1D15	Predose	0:00 ^h			X	
	EOI	1:00				
C2D1	Predose	0:00 ^h			X	
	EOI	1:00				
C2D15	Predose	0:00 ^h				
C3D1	Predose	0:00 ^h		X	X	
	EOI	1:00		X ^d		
Cycle X Day 1	Predose	0:00 ^h			X ^g	
<i>End of Treatment</i>					X	
<i>Follow Up 30 Day</i>					X	
<i>Follow Up 60 Day</i>					X	
<i>Follow Up 90 Day</i>					X	

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 10.5-5: Part 2 (SAR444881 Dose Optimization Cohorts A1 and B1) Pharmacokinetic, Immunogenicity and ECG Sampling

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event ^{a,b}	Hour:Minute Time (Relative to Start of SAR444881 Infusion)		Pembrolizumab PK Serum Sample	ADA Serum Sample	
C1D1	Predose	Before Pembrolizumab Infusion ^k		X	X	
	EOI	1:00		X ^d		
C1D2		24:00 ^e				
C1D8		168:00 ^f				
C2D1	Predose	Before Pembrolizumab Infusion ^k			X	
	EOI	1:00				
C3D1	Predose	Before Pembrolizumab Infusion ^k			X	
	EOI	1:00				
Cycle X Day 1	Predose	Before Pembrolizumab Infusion ^k		X ^h	X ^g	
Cycle X Day 1	EOI	1:00		X ^{d,h}		
<i>End of Treatment</i>					X	
<i>Follow Up 30 Day</i>					X	
<i>Follow Up 60 Day</i>					X	
<i>Follow Up 90 Day</i>					X	

Service	Percentage
Online banking	100%
Mobile banking	85%
ATM	75%
Branch	65%
Phone	55%
In-person	45%

[illegible]

Table 10.8-1: [REDACTED]

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^a	Hour:Minute Time (Relative to Start of SAR444881 Infusion)	[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[illegible]

Table 10.8-2: [REDACTED]

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event ^a	Hour:Minute Time (Relative to Start of SAR444881 Infusion)						

Bar Index	Approximate Length (Percentage of Total Width)
1	95%
2	98%
3	98%
4	75%
5	98%
6	98%
7	20%
8	98%
9	98%
10	85%
11	35%
12	98%
13	25%
14	5%
15	8%
16	8%

Table 10.8-3: [REDACTED]

Study Day of Sample Collection (1 Cycle = every 4 weeks)	Event ^a	Hour:Minute Time (Relative to Start of SAR444881 Infusion)						

[illegible]

Table 10.8-4:

[illegible][illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[illegible]

10.8.2

[REDACTED]

10.8.2.1

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10.8.2.4

[REDACTED]

10.8.2.5

[REDACTED]

[REDACTED]

10.8.2.6 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10.8.3 Use of Biological Samples and Data for Future Research

Future research (research not prespecified by the project team when the protocol is developed and not included in the “drug development program”) may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor’s and/or its affiliates’ and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor’s control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see [Appendix 2](#)) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection – Processing of coded clinical data

The study participant will be provided with all mandatory details of the data processing in Section 9 of the Core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see [Appendix 2](#)).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, i.e., end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (e.g., at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Section 9 of the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.



Table 10.9-1: [REDACTED]

[REDACTED]

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11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

11.1.1 Dose Escalation

In the dose escalation phase (Part 1) a standard “3 + 3” design schema is used [217] for all three sub-parts (SAR444881 monotherapy and SAR444881 combinations; see Section 5.1.2.1). The sample size for the dose escalation phase, which plans to evaluate six dose levels of SAR444881 as a single agent and four dose levels of SAR444881 in combination with pembrolizumab or with cetuximab, was determined by clinical rather than statistical considerations. Cohorts of up to 6 participants will be enrolled at each dose level dependent on an observed DLT. Additional participants may be enrolled in Sub-Parts 1A, 1B and 1C at SAR444881 dose level cohorts of ■ mg/kg and above to better characterize the safety, PK, and pharmacodynamic profiles of SAR444881 (a maximum of 6 additional participants will be enrolled in each dose level).

Up to 156 participants will be treated in Part 1.

11.1.2 Dose Optimization/Expansion

The purpose of dose optimization/expansion (Part 2) is to assess preliminary anti-tumor activity, and collect additional safety, PK and pharmacodynamic information in order to inform the optimal dose of SAR444881.

In Sub-Part 2A (Dose Optimization), 20 participants will be enrolled at one dose level for each indication at Stage 1. For those indications showed activity in Stage 1, 40 participants with 1:1 randomization into two dose levels will be included in the Stage 2. The sample size for each indication will be ranged from 20 to 60 participants. In Sub-Part 2B, 20 participants will be enrolled to receive SAR444881 monotherapy. If activity is observed in these first 20 participants, a further 20 to 40 participants will be enrolled. In total, up to 300 participants will be enrolled in Part 2. Table 11.1-1 lists estimated ORR and the corresponding 95% exact CIs by number of responders.

Table 11.1-1 - Estimated objective response rate (ORR) and 95% CI

Number of responders (N=40)	ORR	95% CI for ORR (Clopper-Pearson)
2	5.0%	(0.6% , 16.9%)
3	7.5%	(1.6% , 20.4%)
4	10.0%	(2.8% , 23.7%)
6	15.0%	(5.7% , 29.8%)
7	17.5%	(7.3% , 32.8%)
8	20.0%	(9.1% , 35.6%)
9	22.5%	(10.8% , 38.5%)
10	25.0%	(12.7% , 41.2%)
11	27.5%	(14.6% , 43.9%)
13	32.5%	(18.6% , 49.1%)
15	37.5%	(22.7% , 54.2%)

With a sample size of 40 study participants for each cohort in Part 2, 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.

11.2 Populations for Analyses

For purposes of analyses, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Intention to treat (ITT)	All participants who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT. Participants will be analyzed according to the treatment arm assigned at randomization and planned dose level (if applicable).
Treated	All participants who receive at least 1 dose of study treatment
Response-evaluable	All treated participants with measurable disease at baseline and one of the following: (a) at least 1 post baseline tumor assessment, (b) clinical progression, (c) death
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have baseline and at least 1 post baseline pre-infusion immunogenicity assessment
Biomarker	All treated participants with available biomarker data

11.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock of first sub parts in dose escalation phase and will describe the statistical analyses and data presentations related to the objectives of the study. Below is a summary of planned statistical analyses. Refer to [Table 4-1](#) and [Table 4-2](#) for a description of primary, secondary, and exploratory endpoints.

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative frequency. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, median, minimum, and maximum and 95% Confidence Interval (CI) for means of variables. The data will be analyzed using the SAS® version 9.4 or higher (SAS Institute, Cary, North Carolina).

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

11.3.1 Efficacy Analyses

Efficacy analyses, listed in [Table 11.3.1-1](#), will be performed on the treated population for the final analysis. In addition, interim efficacy analyses, based on the response-evaluable population, will be performed for each Part 2 optimization/expansion cohort to assess if the observed response rate exceeds the pre-determined futility rate. Interim analyses on efficacy may also be conducted at

various times prior to study completion to facilitate program decisions and to support scientific publications or presentations. Details of the censoring scheme on time-to-event endpoints such as DoR and PFS will be described in the statistical analysis plan.

Table 11.3.1-1: Efficacy Statistical Analysis

Efficacy Endpoint	Statistical Analysis Methods
ORR ORR is defined as the proportion of population of interest whose BOR is either CR or PR. BOR for a participant will be assessed per RECIST v1.1 by Investigator	Estimate of ORR and corresponding 2-sided exact 95% CI based on the Clopper-Pearson method for each tumor type
Median DoR DoR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first	Median duration of response using the Kaplan-Meier method (K-M) and corresponding 2-sided 95% CI (using transformation as appropriate) for each tumor type
PFSR at 3, 6, 9, and 12 and 24 months based on RECIST v1.1 criteria PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first	PFSR Estimate by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula for each tumor type Median PFS using the Kaplan-Meier method and corresponding 2-sided 95% CI as for DoR for each tumor type

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DoR = duration of response; ORR = objective response rate; PFS = progression free survival; PFSR = progression free survival rate; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors

The endpoints based on RECIST v1.1 may also be calculated if warranted based on blinded independent central review assessment. If reported, these will be presented using the same methods as described for the corresponding investigator-based efficacy endpoints.

11.3.2 Safety Analyses

All safety analyses will be performed on the ‘treated’ population, i.e. all participants who have received at least 1 dose of study treatment and will be descriptive in nature.

Safety assessments will include standard laboratory safety tests (hematology, serum chemistry, urinalysis, and others, if applicable), vital signs (blood pressure, heart rate, body temperature, and respiratory rate), physical examinations, 12-lead ECG, AE monitoring, and concomitant medications.

AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Incidences of treatment-emergent AEs (TEAEs, those events that started after exposure to study drug or worsened in severity after dosing) will be presented by treatment group. Incidences of TEAEs will also be presented by maximum severity and relationship to study drug. By-participant listings will be provided for deaths, SAEs, DLTs, and events leading to discontinuation of treatment. Treatment-emergent AEs will be assigned to the dose received preceding event onset. All AEs will be included in the data listings. All AEs will

be listed. The number and percentage of participants reporting AEs, SAEs, study drug-related AEs and AEs leading to withdrawal will be summarized.

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, laboratory data will be graded accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not identified by CTCAE, results will be graded by low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests:

- Frequency table for newly occurring on-treatment Grade 3 or 4
- Shift table using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using low/normal/high/(low and high) classification to compare baseline to worst on-treatment value
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and classifications relative to the laboratory normal ranges

In addition to the above-mentioned tables and listing, other exploratory analysis, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

The following summaries will be generated for ECG analysis:

- Shift table baseline to worst on-treatment result for overall assessments
- Listing of ECG evaluations for all participants with at least one abnormality

Analysis of vital signs will include shift table baseline to worst on-treatment result and table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points. Abnormal physical examination findings will be presented in a by-participant data listing.

Table 11.3.2-1: Safety Endpoints and Analysis

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol defined DLT criteria, AEs leading to discontinuation, and death.	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTCAE grade. Participants will only be counted (1) once at the PT level, (2) once at the system organ class level, and (3) once in the 'total participant' row at their worst CTCAE grade, regardless of system organ class or PT.
Laboratory abnormalities	Laboratory shift table using the worst CTCAE grade on treatment per participant
Laboratory values will be graded according to CTCAE	

v5.0.

Abbreviations: AE = adverse event; CTC = common terminology criteria; CTCAE = common terminology criteria for adverse events; DLTs = dose-limiting toxicities; PT = preferred term; SAE = serious adverse event.

11.3.3 Pharmacokinetic Analyses

Table 11.3.3-1: Pharmacokinetic Endpoints and Analyses

Endpoint	Statistical Analysis Methods
$C_{\max}$, $AUC_{(0-T)}$, $AUC_{(INF)}$, $T_{1/2}$	Summary statistics: includes but not limited to geometric means and coefficients of variation (mean and standard deviation for $T_{1/2}$)
$C_{\max}$	Scatter plots vs dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
$T_{\max}$	Summary statistics: medians and ranges
C_{trough} and C_{eoi}	Summary statistics geometric means and coefficients of variation, by treatment and by day. Scatter plots vs dose for each cycle measured (C_{trough})

Abbreviations: $AUC_{(0-T)}$ = area under the concentration- time curve from time zero to the time of the last quantifiable concentration; $AUC_{(INF)}$ = area under the concentration-time curve from time zero extrapolated to infinite time; $T_{1/2}$ = apparent terminal half-life; C_{eoi} = concentration at the end of infusion; C_{trough} = concentration at the end of the dosing interval. CI = confidence interval; $C_{\max}$ = maximum observed concentration; PK = pharmacokinetic; $T_{\max}$ = time of maximum observed concentration.

Endpoints for PK analyses will be provided as data allows in different part and stage of the studies.

Additional pharmacokinetic analyses, including population PK modelling and pharmacokinetic parameters of pembrolizumab and cetuximab (if analyzed), will be conducted as appropriate or based on statistical analysis plan finalized before database lock.

11.3.4

11.3.5 Immunogenicity

Incidence of ADA to SAR444881 will be assessed using the following endpoints:

- Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline
- ADA-positive participant is a participant with at least one ADA-positive sample relative to baseline after initiation of the treatment
- Presence of neutralizing antibody may be reported, if applicable

The statistical methods used will include frequency distribution of SAR444881 baseline ADA-positive participants and ADA-positive participants after initiation of the treatment. Effect of

11.3.6 Other Analyses

Interim analysis will be planned for each indication in Sub-Part 2A and Sub-Part 2B when 20 participants have undergone at least two post-baseline tumor assessments or have discontinued the study intervention. Analysis based on totality of data (including efficacy, safety, PK and PD) for each cohort will be conducted to determine whether to move to Stage 2 for dose optimization in Sub-Part 2A and whether to enroll additional 20 participants in Sub-Part 2B.

Table 11.3.7-1: Bayesian toxicity monitoring plan in dose optimization/expansion phase

[illegible]

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12 APPENDICES

Appendix 1 Abbreviations and Trademarks

Term	Definition
AE	adverse event
AESI	adverse event of special interest
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC _(TAU) at steady state to AUC _(TAU) after the first dose
AI_C _{max}	C _{max} Accumulation Index; ratio of C _{max} at steady state to C _{max} after the first dose
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AT	aminotransaminases
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC _(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC _(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC _(TAU)	area under the concentration-time curve in one dosing interval
AxMP	auxiliary medicinal product
β-HCG	beta-human chorionic gonadotrophin
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
C	Celsius
Ca ⁺⁺	calcium
C _{avg}	average concentration
CBC	complete blood count

Term	Definition
CFR	Code of Federal Regulations
CI	confidence interval
Cl ⁻	Chloride
CL _{cr}	creatinine clearance
Cm	Centimeter
C _{max}	maximum observed concentration
C _{min}	minimum observed concentration
CNS	central nervous system
CRC	colorectal cancer
CRF	Case Report Form, paper or electronic
CRS	cytokine release syndrome
CTAg	Clinical Trial Agreement
C _{trough}	Concentration at the end of the dosing interval
CV	coefficient of variation
DC	dendritic cells
DO	dose optimization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e.g.	exempli gratia (for example)
ESR	Expedited Safety Report
F	Bioavailability
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
G	Gram
GA	global alternative
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GN	global null

Term	Definition
H	Hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	hazard ratio
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
i.e.	id est (that is)
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IMP/IP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	Intravenous
K ⁺	Potassium
kg	Kilogram
L	Liter
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
LFTs	liver function tests
MAAD	maximum administered dose
mAb	monoclonal antibody
mg	Milligram
Mg ⁺⁺	Magnesium
min	Minute

Term	Definition
mL	Milliliter
mmHg	millimeters of mercury
MR	medical research
MRI	Magnetic resonance imaging
msec	Millisecond
MTD	maximum tolerated dose
µg	Microgram
N, n	number of subjects or observations
Na ⁺	Sodium
N/A	not applicable
ng	Nanogram
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PD	Pharmacodynamics, progressive disease
PK	Pharmacokinetics
PO	per os (by mouth route of administration)
PoC	proof-of-concept
████	████████████████████
QC	quality control
QD, qd	quaque die, once daily
Q2W	every 2 weeks
R ²	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SOP	Standard Operating Procedures
sp.	Species
SRC	Safety Review Committee
Subj	Subject

Term	Definition
t	Temperature
T	Time
T _{1/2}	half life
T _{max}	time of maximum observed concentration
TNBC	Triple negative breast cancer
ULN	upper limits of normal
UV	Ultraviolet
V _{ss} /F (or V _{ss})	apparent volume of distribution at steady state
W	Washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women <u>not</u> of childbearing potential

Appendix 2 Study Governance Considerations

The term ‘Participant’ is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term ‘Subject’ used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable, United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- The General Data Protection Regulation (GDPR) and any other applicable data protection laws
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

Responsibility of Investigators includes providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014

of the European Parliament and the Council of the European Union for clinical studies, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g. loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (e.g. advertisements), and any other written information to be provided to subjects. The Investigator or Sanofi should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling information to be provided to subjects and any updates.

The Investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g. expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to Sanofi.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health 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.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (i.e. Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in

which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.
- Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent.
- The Investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study.
- Fully document the informed consent process in the subject's medical records, including study reference, subject number, date, who consented the subject and any additional copy of the signed ICF given to the subject/legally authorized representative.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that Sanofi and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

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 responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sponsor databases, including trial participants, 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 personal data

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

“Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (e.g., 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, when applicable, 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.
- Participants must be informed that their 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.
- Participants must be informed that their 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.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (e.g., Sponsor’s personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole “drug development program”, i.e., 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.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records.

STUDY/SITE TERMINATION

The Sponsor or designee reserves the right to close the study site or terminate the study 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 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 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 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.

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by Sanofi, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of Sanofi/designee or a Health Authority.

If...	Then...
Supplied by Sanofi (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g. lost, wasted) • amount destroyed at study site, if applicable • amount returned to Sanofi • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability
Sourced by site, and not supplied by Sanofi or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

Sanofi or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a sub investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the electronic data capture tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of Sanofi or designee must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Sanofi audit reports will be kept confidential.

The Investigator must notify Sanofi promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The Investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by Sanofi or designee, whichever is longer. The Investigator must contact Sanofi prior to destroying any records associated with the study.

Sanofi or designee will notify the Investigator when the study records are no longer needed.

If the Investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another investigator, study site, IRB). Notice of such transfer will be given in writing to Sanofi or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by Sanofi, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If...	Then...
Study treatments supplied by Sanofi (including its vendors)	Any unused study treatments supplied by Sanofi can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g. cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by Sanofi (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the Investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the Investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to Sanofi upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the Investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by Sanofi (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by Sanofi, is solely the responsibility of the Investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

A Signatory Investigator must be selected to sign the clinical study report. For this protocol, the Signatory Investigator will be the External Principal Investigator designated at protocol development.

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

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, euclinicaltrial.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (i.e., the last active, participating country).

In addition, results from clinical trials in participants 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 vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. 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: vivli.org.

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”.

Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) that is:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI
- Any abnormal other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (e.g. not related to progression of underlying disease, or more severe than expected for the participant's condition), e.g.:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the IMP.
- "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 fulfil the definition of 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 (e.g. 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.

SERIOUS ADVERSE EVENTS

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

1. Results in death;
2. Is life-threatening (defined as 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);
3. Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below);

NOTE:

The following hospitalizations are not considered SAEs in Sanofi clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on

health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

4. Results in persistent or significant disability/incapacity;

5. Is a congenital anomaly/birth defect; or

6. Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 10.2.6](#) for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to Sanofi as used for SAEs (see [Section 10.2.4](#) for reporting pregnancies).

EVALUATING AEs AND SAEs

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE and will determine whether or not an adverse event is considered to be related to the study drug
- 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) 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 Sponsor. 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 Sponsor.
- 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.

Assessment of Severity

The adverse event severity grading scale CTCAE v5.0 will be used to assess adverse events severity. [Table APP-3-1](#) will be used for assessing severity for adverse events that are not specifically listed in the CTCAE.

Table APP-3-1: Adverse Event Severity Grading Scale	
Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living ^a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living ^b
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event

^a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

Follow-up of AEs and SAEs

- If only limited information is initially available, follow-up reports are required. (Note: follow-up SAE reports must include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Sanofi (or designee) using the same procedure used for transmitting the initial SAE report.
- All AEs must be followed to resolution, stabilization, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- During the study period, resolution of adverse events (with dates) should be documented on the Adverse Events CRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Events CRF.
- For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g. from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

REPORTING OF SAEs TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to Sanofi (or designee) within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).
- The preferred method for SAE data collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms will be used when the eCRF system is not functioning or does not support electronic submission of reports.
 - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Study Contact Information list.

SAE Facsimile Number: Refer to Study Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for all SAEs and Pregnancy reporting): Refer to Study Contact Information list.

Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy

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

- Postmenopausal female
 - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 10 months after the end of study treatment for females and 7 months for males.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly.^a

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b
 - oral
 - intravaginal
 - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation^b
 - oral
 - injectable

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation^b
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)^c
- Intrauterine device (IUD)^c
- Bilateral tubal occlusion
- Vasectomized partner
A vasectomized partner is a highly effective contraception method provided that the partner is the sole male 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.
- 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 treatment. 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.
- It is not necessary to use any other method of contraception when complete abstinence is elected.

- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in [Section 2](#).
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

NOTES:

- ^a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
- ^b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.
- ^c Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 7 months after the end of study treatment
- Female partners of males participating in the study should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of study treatment in the male participant
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in [Section 10.2.4](#) and in [Appendix 3](#) for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

Appendix 5 ECOG Performance Status

ECOG PERFORMANCE STATUS ^a	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

^a Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

Appendix 6 SAR444881-related immune-mediated Adverse Events Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. Management algorithms were developed based on algorithms of approved immuno-oncology (I-O) drugs [4, 5, 220] and are intended to assist investigators in assessing and managing immune-mediated AEs (imAEs). The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Based on the severity of the adverse reaction, permanently discontinue or withhold SAR444881 when studied as a single agent and SAR444881 and pembrolizumab when studied in combination, [REDACTED]. imAEs have been reported to occur after discontinuation of immune checkpoint blockade therapy.

Corticosteroids are the primary treatment for immuno-oncology drug-related immune adverse events. Importantly, [REDACTED] to treat imAEs has not been shown to reduce antitumor efficacy. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of [REDACTED] should be taken into account when switching to the [REDACTED]. Upon improvement to [REDACTED] should be initiated and continued over at least [REDACTED]. [REDACTED] is recommended to adequately resolve toxicity and prevent recurrence. Restarting SAR444881 and pembrolizumab should be considered after completion of [REDACTED] based on the severity of the event (see [Section 9.2](#)). [REDACTED] imAEs may require administration of additional [REDACTED]. Close monitoring and follow-up should be performed to assess for [REDACTED] in the setting of imAEs. Permanently discontinue SAR444881 and pembrolizumab if no complete or partial resolution of imAEs within 12 weeks of initiating steroids or inability to [REDACTED] or less (or equivalent) within [REDACTED] weeks of initiating steroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

Management of immune-mediated colitis and gastrointestinal adverse reactions

Grade of [REDACTED]	Management	Follow Up
[REDACTED]		

In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded. Cytomegalovirus (CMV) infection/reactivation has been reported in patients treated with PD-1 blockade who developed corticosteroid-refractory immune-mediated colitis.

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]s

Management of immune-mediated nephritis and renal adverse reactions

[illegible]

Management of [REDACTED] adverse reactions

Grade of [REDACTED]	Management	Follow Up
[REDACTED]		

*Grades correspond to those listed in the NCI CTCAE Version 5.0 †Resume treatment when adverse reaction returns to Grade 0 or 1 ‡Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at the start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids §Add prophylactic antibiotics for opportunistic infections ||Consider adding prophylactic antibiotics

IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Management of immune-mediated hepatic adverse reactions for patients with tumor involvement of the liver

- For participants with tumor involvement of the liver, permanently discontinue, withhold, or continue treatment based on the severity of immune-mediated hepatitis and baseline AST and ALT levels as described below.
- In addition, administer [REDACTED] prednisone equivalents, followed by [REDACTED] [REDACTED] when treatment is withheld or discontinued due to immune-mediated hepatitis.
- If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue treatment based on recommendations for hepatic adverse reactions with no liver involvement.

Severity*	Dose modification
[REDACTED]	

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 †Resume treatment if AST/ALT returns to baseline.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; HCC=hepatocellular carcinoma; ULN=upper limit of normal.

Management of immune-mediated hepatic adverse reactions for participants with no tumor involvement of the liver

Grade of Liver Function Tests Elevation*	Management	Follow Up

*Grades correspond to those listed in the NCI CTCAE Version 4.0 †Resume treatment when adverse reaction returns to Grade 0 or 1 ‡Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids §Add prophylactic antibiotics for opportunistic infections ||Consider prophylactic antibiotics for opportunistic infections and resume immunotherapy per protocol

ALT=alanine aminotransferase; AST=aspartate aminotransferase; HCC=hepatocellular carcinoma; IV=intravenous; LFT=liver function test; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; T. bili=total bilirubin; ULN=upper limit of normal.

Management of immune-mediated endocrinopathies

	Hypophysitis ¹	Adrenal insufficiency ²	Hypothyroidism/thyroiditis or hyperthyroidism	Type 1 diabetes mellitus

1. **Hypophysitis NCI CTCAE grading** (version 4.0): Grade 1: 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 ADL; Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL; Grade 4: Life-threatening consequences; urgent intervention indicated

2. **Adrenal insufficiency NCI CTCAE grading** (version 4.0): Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated; Grade 2: Moderate symptoms; medical intervention indicated; Grade 3: Severe symptoms; hospitalization indicated; Grade 4:

Life-threatening consequences; urgent intervention indicated

*Resume treatment when adverse reaction returns to Grade 0 or 1 †Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids *Consider prophylactic antibiotics for opportunistic infections

IV=intravenous; MRI=magnetic resonance imaging; ADL=activities of daily living; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

Management of immune-mediated skin adverse reactions

Grade of Skin Adverse Reactions*	Management	Follow Up

*Grades correspond to those listed in the NCI CTCAE Version 4.0 †Resume treatment when adverse reaction returns to Grade 0 or 1 ‡Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids §Add prophylactic antibiotics for opportunistic infections

BSA=body surface area; IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis.

Management of immune-mediated encephalitis and neurologic adverse reactions

- Withhold treatment in participants with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration.
- If other etiologies are ruled out, [REDACTED]s for participants with immune-mediated encephalitis, followed by [REDACTED].
- Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Grade of Neurologic Adverse Reactions*	Management	Follow Up
[REDACTED]		

*Grades correspond to those listed in the NCI CTCAE Version 4.0 †Resume treatment when adverse reaction returns to Grade 0 or 1 ‡Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids §Add prophylactic antibiotics for opportunistic infections

IV=intravenous; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

Appendix 7 Tumor Response Assessment

1. EVALUATION OF LESIONS

Tumors will be evaluated during the study using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline [224].

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1. Measurable Lesions

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or $\geq 2 \times$ slice thickness if greater than 5 mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by malignant cells. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumors. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray imaging are not to be selected as Target or Non-Target Lesions.

1.2. Non-Measurable Lesions

All other lesions are considered non-measurable, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3. Bone lesions measurability

- Bone scan, PET scan and plain films are **not** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4. Baseline Documentation Of ‘Target’ And ‘Non-Target’ Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where participants have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected based on 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 as noted above, 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.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details below). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2. RESPONSE CRITERIA

2.1. 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.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of 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. (Note: the appearance of one or more new lesions is also considered progression).
- **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.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1. Special Notes on the Assessment of Target Lesions

2.1.1.1. Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2. Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. 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 as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3. Lesions that split or coalesce on treatment

When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

2.2. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1. Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1. When the patient also has measurable disease

In this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2. When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable

disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.2. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. 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:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

2. 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.

2.3. Response Assessment

2.3.1. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.3.2. Time Point Response

At each protocol specified time point, a response assessment occurs. [Table APP-7-2.3.2-1](#) provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline. When participants have non-measurable (therefore non-target) disease only, [Table APP-7-2.3.2-2](#) is to be used.

Table APP-7-2.3.2-1: Time Point Response: Participants with Target (± Non-Target) Disease			
Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = Not Evaluable

Table APP-7-2.3.2-2: Time Point Response: Participants with Non-target Disease Only		
Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD ^a
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = Complete Response, PD = Progressive Disease, NE = Not Evaluable

^a Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3. Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in [Table APP-7-2.3.3-1](#).

When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date. In the current study the first scheduled follow-up imaging visit is Week 8 (± 7 days); a Best Response of SD can only be made after the subject is on-study for a minimum of 8 weeks (56 days) minus 7 days, for an absolute minimum time on-study of 49 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to ‘normal’ size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of ‘zero’ on the case report form (CRF).

Table APP-7-2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD

Table APP-7-2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = Not Evaluable		

^a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4. Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (e.g. CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g. PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

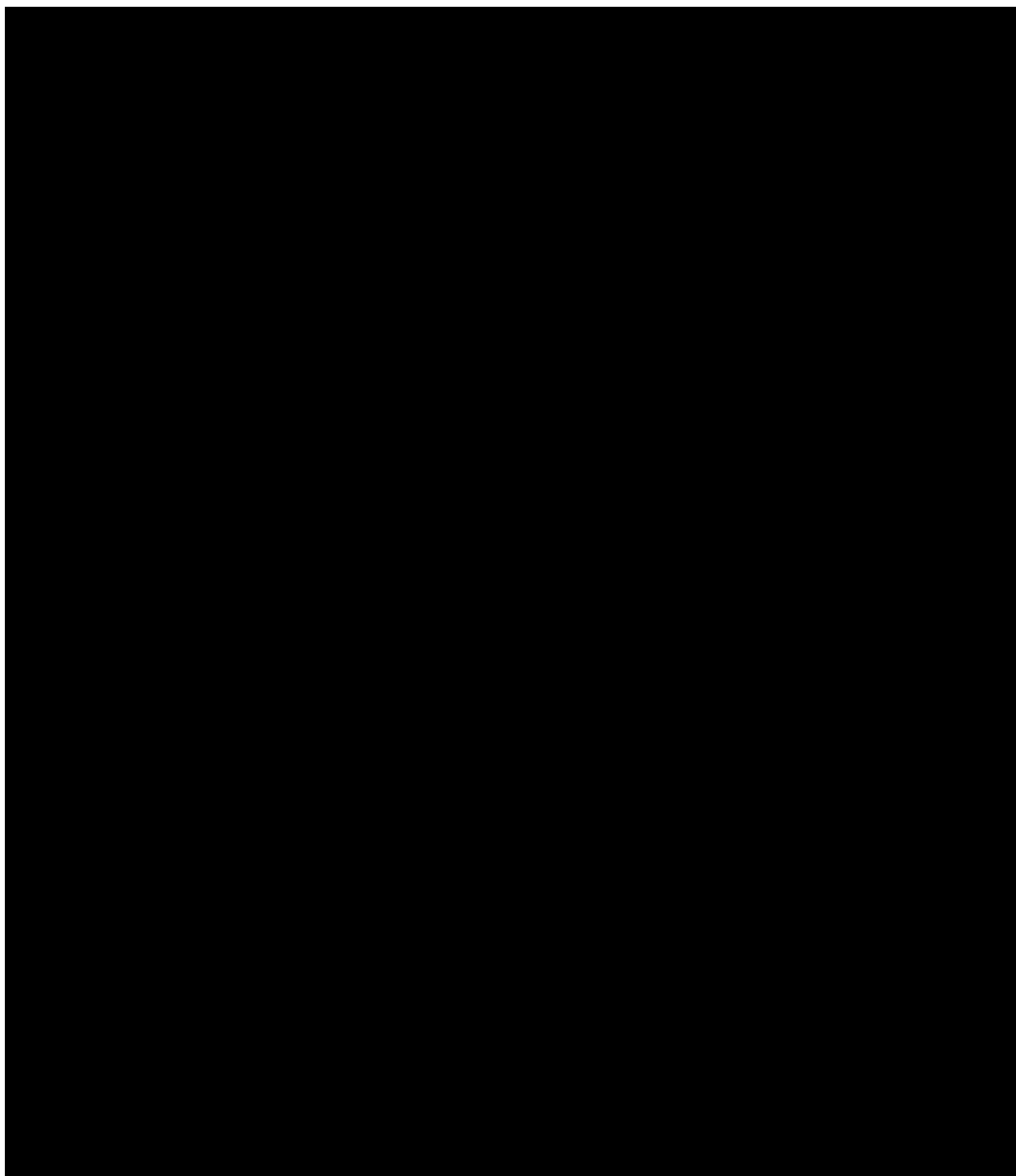
Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

Appendix 8

[REDACTED]

[REDACTED]

[REDACTED]



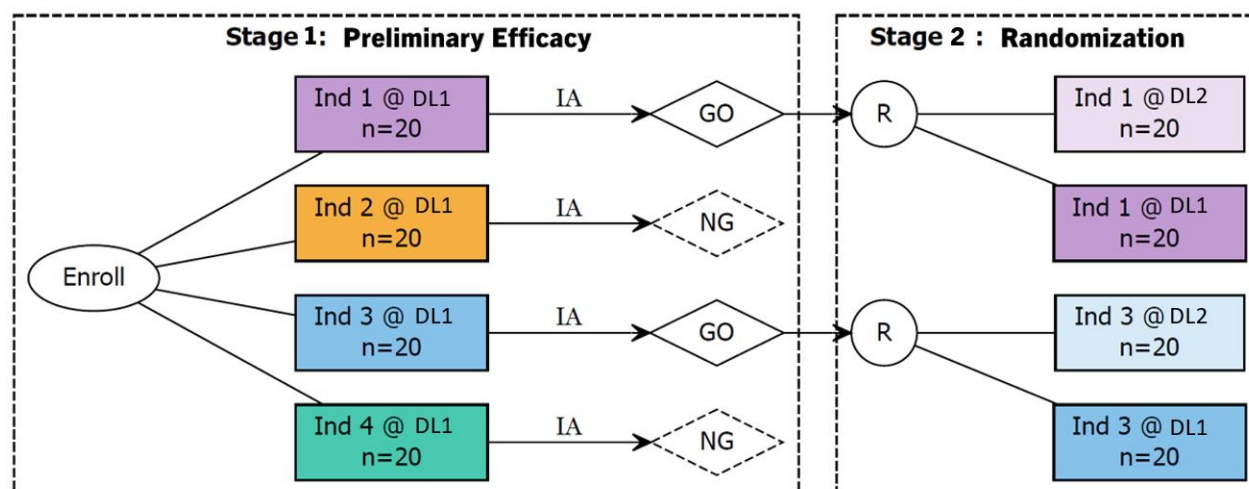
Appendix 9 Two-Stage Design

The Sponsor will conduct a comprehensive evaluation of the totality of dose escalation data, including preliminary activity (e.g., ORR, PFS, duration of treatment), safety and PK/PD to select an optimal dose. With ORR as primary endpoint for evaluating efficacy, the Sponsor proposes a Two-stage design for dose optimization.

1. Overall design and analysis plan

The design schema is illustrated in Figure APP-9-1, where Stage 1 aims to evaluate preliminary efficacy in each selected indication at a dose that is determined safe and potentially active based on totality of data from dose escalation, followed by a Stage 2 to optimize between the Stage 1 dose (DL1) and a second dose (DL2) in a 1:1 randomized setting. An interim analysis at the end of Stage 1 will determine which indication(s) and dose levels, if any, will move on to Stage 2 for dose optimization, while other indication(s) or a dose level may be stopped for early futility. The key principle for the design utilizing a Bayesian hierarchical model is to first identify indication(s), if any, that show preliminary efficacy for further dose optimization, while during the dose optimization stage the higher dose will be selected only when it shows substantially better activity (as demonstrated as ORR in this case) than the lower dose, given that the other aspects, including safety and PK/PD, are comparable. Otherwise, the lower dose will be selected for the comparable activity at similar safety and PK/PD.

Figure APP-9-1 - The Two-stage design schema with hypothetical two GO & two No-Go of indications after Stage 1



Abbreviations: Ind: indication; DL1: Dose at Stage 1; DL2: the second dose at Stage 2; IA: interim analysis; NG: no-go; R: randomization.

Denote τ_1 as the target log-odds difference we wish to distinguish between ORR of the investigational treatment regimen and the reference ORR demonstrated by the current standard of care (the same regardless of dose). And denote τ_2 as the target log-odds difference we wish to distinguish between the ORRs of the two dose levels. There are four decision criteria used in the Two-stage design (ORRs are on some appropriate logit transformations):

- 1) Determine activity of DL1 in Stage 1: $P(\text{ORR}_1 \geq \tau_1 | \text{Stage 1 data}) > s_1$;
- 2) Determine activity of DL1 in Stage 2: $P(\text{ORR}_1 \geq \tau_1 | \text{Stage 1\&2 data}) > s_2$;

- 3) Determine activity of DL2 in Stage 2: $P(\text{ORR}_2 \geq \tau_1 | \text{Stage 2 data}) > t_2$;
4) Dose optimization between two doses: $P(|\text{ORR}_1 - \text{ORR}_2| \geq \tau_2 | \text{Stage 1\&2 data}) > w_2$.

For these criteria mentioned above, τ_1 is determined by the reference ORR and target ORR which is the minimum response rate for which we consider the investigational drug to be efficacious. The reference and target ORRs of the four indications in this study are listed in Table APP-9-1. The indication-specific reference ORRs range from [REDACTED], and target ORRs range from [REDACTED]. The value of the tuning parameter τ_2 is determined by the possible ORR(s) for the lower dose and the minimum difference in ORRs to be distinguished between the two doses in the dose optimization. s_1 , s_2 , t_2 and w_2 are tuning parameters with [REDACTED] usually set as initial value for each parameter and can be adjusted by simulation studies to generate desirable frequentist operating characteristics (e.g., familywise type I error less than [REDACTED]).

Table APP-9-1 - Reference and target ORRs for each indication

Indication	Combination Therapy	Reference ORR	Target ORR
Non-squamous NSCLC	SAR444881 + pembrolizumab + carboplatin + pemetrexed as 1L therapy	[REDACTED]	[REDACTED]
NSCLC	SAR444881 + cetuximab as 2L and later therapy	[REDACTED]	[REDACTED]
GC/GEJ	SAR444881 + pembrolizumab as 3L and later therapy	[REDACTED]	[REDACTED]
CRC any RAS	SAR444881 + cetuximab as a 3L and later therapy	[REDACTED]	[REDACTED]

At the end of Stage 1, for each indication, an interim analysis will be conducted when 20 participants have undergone at least two post-baseline tumor assessments or have discontinued the study intervention. The posterior probability of $\text{ORR}_1 \geq \tau_1$ will be calculated. A Go decision will be made to continue to Stage 2 for this indication when the probability is greater than s_1 , otherwise the indication may be stopped.

For each indication moved to Stage 2, final analysis will be conducted when additional 20 participants in DL1 and 20 participants in DL2 have undergone at least two post-baseline tumor assessments or have discontinued the study intervention. The decision criteria from 2) to 4) will be evaluated. Criteria 2) and 3) are used to determine the proof-of-concept for DL1 and DL2 respectively. If criteria 2) and 3) are not met, then neither dose will be selected. This indication will be stopped for futility. If one of criteria 2) or 3) is met, then the corresponding dose will be selected for the corresponding indication for further development. If both 2) and 3) are met, then criterion 4) is used to select the dose that demonstrates better efficacy as the optimal dose in the corresponding indication.

2. Simulation study

Comprehensive simulations are performed to evaluate the performance (operating characteristics) of the Two-stage design. The objective response rate (ORR) assumptions for DL1 and DL2 across all four indications are tabulated in Table APP-9-2. From the perspective of detecting preliminary efficacy signal, the scenarios cover not only the global null (GN) case (where all treatments in the

four indications are inefficacious) and the global alternative (GA) case (where all treatments in the four indications are efficacious), but also a variety of intermediate situations where only treatments in some indications are efficacious. From the perspective of distinguishing the better treatment effect between the two doses, the scenarios cover cases where the higher or lower dose should be selected for certain indications (Pick-H-Partial and Pick-L-Partial scenarios, respectively), or a mixture of higher dose for certain indications while lower dose for others (Mixed scenario). In each scenario, we set $s_1 = s_2$ [REDACTED], $t_2 = w_2 =$ [REDACTED]. The minimum difference in ORRs to be distinguished between the two doses is set to be [REDACTED].

Table APP-9-2 - Simulation scenarios of true ORRs for evaluating operating characteristics of Two-stage design

Scenario	Dose	Indication 1	Indication 2	Indication 3	Indication 4
GN	DL1	[REDACTED]			
	DL2				
GA	DL1				
	DL2				
Pick-H-Partial	DL1				
	DL2				
Pick-L-Partial	DL1				
	DL2				
Mixed	DL1				
	DL2				

Abbreviations: GN: Global Null; GA: Global Alternative; H: higher dose; L: lower dose.

Text in green means the indication at this dose level should be selected as Go at final analysis.

Text in red means the indication at this dose should be No-Go.

Results for the interim analysis at the end of Stage 1 are shown in [Table APP-9-3](#). For each scenario, the probability of making a Go decision to move from Stage 1 to Stage 2 is calculated by indication. For unpromising indications across all scenarios, the probabilities of making a Go decision are all kept below 10%, while the probabilities of moving from Stage 1 to Stage 2 for those promising indications range from 57.3% to 79.3%.

Table APP-9-3 - Stage 1 simulation results

	Stage 1: probability of making a Go decision to move to Stage 2 (by indication)			
Scenario\Indication	Indication 1	Indication 2	Indication 3	Indication 4
GN	[REDACTED]			
GA				
Pick-H-Partial				
Pick-L-Partial				
Mixed				

GN: Global Null; GA: Global Alternative; H: higher dose; L: lower dose.
Text in red means the indication at this dose should be No-Go after Stage 1.

End-of-trial (end of Stage 2) results are shown in Table APP-9-4. Not only the “by-indication” metrics for proof-of-concept (PoC) and dose optimization (DO) but also familywise type I error or powers are reported. Familywise type I error is the probability of making false Go decision in at least one indication at the end of Stage 2 under the global null scenario.

There are a few key messages:

- Overall, the familywise type I error is well-controlled at 0.148 under the global null scenario. For the other scenarios, the probabilities that at least one promising indication is selected as proof-of-concept are satisfactory (range: [REDACTED]). For dose optimization, the probabilities that the optimal dose in at least one indication is selected for further development are also satisfactory (range: [REDACTED]).
- Because of the early futility interim analysis at the end of Stage 1, the probability of advancing an unpromising indication for further development at the end of trial is extremely low across all scenarios.
- The by-indication powers for proof-of-concept (range: [REDACTED]) and dose optimization (range: [REDACTED]) for the promising indications are also acceptable in most of the scenarios.

Table APP-9-4 - End-of-trial simulation results

	End-of-trial (end of Stage 2)								
	By-indication Type I error or power for proof-of-concept(PoC)				By-indication Type I error or power for dose optimization(DO)				Familywise Type I error or power
Scenario\ Indication	Ind 1	Ind 2	Ind 3	Ind 4	Ind 1	Ind 2	Ind 3	Ind 4	
GN									
GA									
Pick-H-Partial									
Pick-L-Partial									
Mixed									

GN: Global Null; GA: Global Alternative; H: higher dose; L: lower dose; Ind: Indication.
Number in red is type 1 error.

In case when other measures (e.g., safety, tolerability, PK/PD, etc.) are relatively comparable between the two doses, the Two-stage design, as demonstrated by the simulation results above, provides a viable solution to the identification of the optimal dose based on the efficacy endpoint of ORR.

Appendix 10 Country-Specific/Region Requirements

1. Germany

Informed consent process: All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in [Section 10.2](#) and [Appendix 2](#).

2. France

Exclusion criterion specific to France:

- 6) The participant is not affiliated to a social security scheme.
- 7) The participant is under tutorship or curatorship; the participant is under safeguard of justice or deprived of his/her liberty by an administrative or court decision.

3. European Union

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

A single Annual Safety Report, aligned with ICH E2F, will include safety information for all IMPs (including the reference compound[s]).

Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC, irrespective if they are used in accordance with the terms of the marketing authorizations of these products. The Investigator is requested to report any suspected adverse reactions assessed as solely related to an authorized AxMP to the National Competent Authority via the national reporting system.

Appendix 11 Contingency Measures for a Regional or National Emergency that is Declared by a Governmental Agency

For Germany contingency measures are currently only applicable for the COVID-19 pandemic.

Appendix 12 Collection, Storage and Future Use of Data and Human Biological Samples

1. Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately for studies conducted in European countries.

2. Compliance with Member State applicable rules for the collection, storage and future use of personal data (article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately for studies conducted in European countries.

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