

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 1 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : [REDACTED] REVISION NUMBER : 3.0

Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	10-JUL-2022	Original Release	[REDACTED] [REDACTED], BST
2.0	23-JAN-2023	Protocol Amendment (Protocol V5): Primary reason: addition of a BND-22 dose level (20 mg/kg) in the Dose Escalation phase	[REDACTED] BST
3.0	30-NOV-2023	Current SAP is specific to Study Sub-Part 1A	[REDACTED] BST

NCT04717375

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 2 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

Dose Escalation (Study Sub-Parts 1A)

— Statistical Analysis Plan

Study Title: A Phase 1/2, dose escalation and expansion study of the safety, tolerability, and anti-tumor activity of BND-22 administered alone and in combination with pembrolizumab or with cetuximab in patients with advanced solid tumors

Protocol Identifier: BND-22-001(TCD17465) (Study Sub-Part 1A only)

Study Drug: BND-22 (SAR444881)

Sponsor: Biond Biologics for Sanofi-Aventis Recherche & Développement

SAP Version Number: Version 3: 30-Nov-2023



	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 3 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

1. TABLE OF CONTENTS

1. DEFINITIONS AND/OR ABBREVIATIONS 4

2. PURPOSE..... 6

3. SCOPE 6

4. RESPONSIBILITIES 7

5. PROCEDURE..... 8

6. RELATED DOCUMENTS 21

7. RELATED FORMS..... 21

8. APPENDICES 21

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 4 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

1. DEFINITIONS AND/OR ABBREVIATIONS

AE	Adverse event
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
BL	Baseline
C _{ei}	Concentration at the end of infusion
CI	Confidence Interval
C _{max} , C _{MAX}	maximum observed concentration
CRF	Case Report Form (may be paper or electronic representation of the data collection tool)
CRO	Contract Research Organization
C _{tau}	Plasma concentration at the end of the dosing interval
C _{trough}	Trough observed plasma concentration
FDA	Food and Drug Administration
Hr(s)	Hour(s)
ICF	Informed Consent Form
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
mm	millimeter

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 5 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

NA	Not applicable
PI	Primary Investigator
PT	Preferred Term
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD / STD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
WHO	World Health Organization coding system for medications

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 6 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

2. PURPOSE

- 2.1 The purpose of this document is to describe in detail the Statistical Analysis Plan of clinical study procedures carried out by Medistat Ltd.
- 2.2 This document serves Medistat Ltd. as a guiding document for all statistical analyses performed at the end of each clinical study.
- 2.3 This SAP is specific to study BND-22-001 (TCD17456) Study Sub-Part 1A sponsored by Biond Biologics for Sanofi-Aventis Recherche & Développement.
- 2.4 This SAP aims to provide details on: sample size calculation, efficacy analyses and safety analyses.

3. SCOPE

- 3.1 This document applies to all members of the statistical & data management units in Medistat Ltd.
- 3.2 This document includes the main and interim study trial analysis.

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 7 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

4. RESPONSIBILITIES

4.1 Medistat Ltd. Responsibilities

The following personnel are responsible for these activities:

Activities	Responsible and accountable	Title
Statistical Analysis Plan (SAP)		Senior Biostatistician & SAS Programmer
Statistical Report and listing		Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of SAP		Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of programs and final report		Quality & Data Assurance Manager

4.1 Biond Biologics Responsibilities

- 4.1.1 To review and approve the SAP and related documents prior to database freeze for Sub-Part 1A escalation cohort analysis .

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 8 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

5. PROCEDURE

5.1 Introduction

This Statistical Analysis Plan (SAP) is based on the study protocol final version 5.2 dated July 13th 2023.

This SAP contains details of the statistical analyses that will be performed, providing a more detailed description of the approach defined in the study protocol. Definitions of variables and populations used for the analyses are also included. The SAP will be finalized and signed prior to database lock for Sub-Part 1A of Escalation phase. This SAP describes planned statistical analyses of clinical data collected in the dose escalation phase of study BND-22-001 (TCD17465) Sub-Part 1A. The planned analyses of data collected in the Sub-Parts 1B and 1C and in dose expansion phase (Part 2) of the study will be described in separate SAP document.

General output specifications are provided; examples are given of calculations of derived variables.

5.2 Study Rationale

Based on nonclinical data, treatment with BND-22 (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. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

Study BND-22-001 is the first-in-human study of BND-22. It is an open-label, multicenter, dose escalation and expansion study designed to evaluate the safety and tolerability of BND-22 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 BND-22 monotherapy and collect additional data that will inform future clinical development – the study is designed to also characterize the PK profile of BND-22 and to explore potential associations between anti-tumor activity of BND-22 and select [REDACTED] measures in the [REDACTED]

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 9 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

5.3 Study Objectives and Endpoints

Dose Escalation (Study Sub-Parts 1A)

Objectives relative to Sub- Part 1A	Endpoints
Primary 1. To assess the safety and tolerability of BND-22 when administered alone To determine the MTD or MAAD and the Recommended Phase 2 Dose (RP2D) of BND-22 when administered alone	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 BND-22 monotherapy) 1. To assess preliminary anti-tumor activity of BND-22 2. To characterize the PK of BND-22 3. To characterize the immunogenicity of BND-22	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 BND-22 (C_{max} , C_{tau} , T_{max} , $T_{1/2}$, AUC) 3. Incidence of anti-drug antibodies (ADA), including neutralizing ADA (nADA), to BND-22
Exploratory	

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 10 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

5.4 Randomization, Blinding and Un-blinding

This is an open label, non-randomized study.

5.5 Selection of study population

The study will enroll up to 258 participants overall (up to 156 in Part 1 and up to 102 in Part 2)

Part 1 (BND-22 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 (Dose Limiting Toxicity (DLT)) observations. Up to 60 participants will be treated in Sub-Part 1A (BND-22 single agent dose escalation). This number 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 BND-22 (the study allows enrollment of 6 additional participants in the higher dose level cohorts; see Section 5.1.2.1 of study protocol).

5.6 Sample Size Justification

In the dose escalation phase Study Sub-Part 1A a standard "3 + 3" design schema is used. The sample size for the dose escalation phase, which plans to evaluate up to five dose levels of BND-22 as a single agent, 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 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg dose levels to better characterize the safety, PK, and pharmacodynamic profiles of BND-22 (a maximum of 6 additional participants will be enrolled in each dose levels).

Up to 60 participants will be treated in Sub-Part 1A.

5.7 Statistical Analysis Software and Data Management

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® version 9.4 or higher for Windows.

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 11 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

Data Management

The Trial Master system is used in the study for data collecting and management. The system is designed, developed, and installed by MediStat.

Edit checks are performed for the purpose of ensuring the accuracy, integrity, and validity of the database. These edit checks may include missing value checks, range checks, consistency, sequence and protocol adherence checks.

Medical Coding

Concomitant medications entered into the database are coded using the WHO (World Health Organization) Drug Public Website Dictionary named WHOCC-ATC/DDD index, which employs the Anatomical Therapeutic Chemical classification system.

Adverse events and Medical History are coded using the most updated version of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Handling of Missing data

No imputation will be applied for missing data

Protocol Violations and Deviations

Protocol violations and deviations will be listed.

5.8 Subject Population for analyses

The Enrolled population will include all Sub-Part 1A participants who signed the informed consent form.

The Treated population will include Sub-Part 1A participants who receive at least 1 dose of study treatment.

The Response-evaluable population will include all treated Sub-Part 1A participants with measurable disease at baseline and one of the following: (a) at least 1 post baseline tumor assessment, (b) clinical progression, (c) death.

6. STUDY SUB-PART 1A STATISTICAL ANALYSIS

6.1 General

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

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 12 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

tables will be provided giving sample size, arithmetic mean, standard deviation, median, minimum and maximum and 95% CI (Confidence Interval) for means of variables.

The data is analyzed using the SAS ® version 9.4 or higher (SAS Institute, Cary North Carolina). Analyses presented in the clinical report but not mentioned in the SAP are unplanned or ad-hoc analyses.

Statistical methods presented in the SAP may be slightly different from those that are presented in the protocol. Differences are clearly stated and the SAP supersedes the protocol only with regard to the way data will be handled and analysed.

Derived Data

Definition of baseline - Baseline is defined as the last non-missing value prior to the patient start of treatment (screening or pre-administration value of first treatment visit).

End of Study - The end-of-study visit is defined as the last follow up safety visit or last visit in subjects who do not complete the study.

Incomplete dates

All incomplete dates will be entered in the database as they were recorded in the EDC. Thereafter, for calculation purposes, the incomplete dates will be completed using pre-defined rules.

If a day or month is recorded as UNK it will be replaced by the first day of the month or January, respectively, provided this does not contradict any other dates recorded. If both day and month are recorded as UNK it will be replaced by the first day of month and January.

Demographic and Baseline data

Baseline and demographic data will be summarized in appropriate tables using the Treated population. The data includes demographic characteristics (age, gender, ethnicity and race), medical history, drug and tobacco use, disease related medical history and number of previous treatment lines.

Disposition of subjects

The number of subjects that are randomized into Sub-Part 1A, the number of subjects in the Enrolled, Treated and Response-evaluable populations, the number of study completers, and the number of participants in escalation cohorts who were evaluable for Dose Limiting Toxicity (DLT) assessment will be presented.

The reasons for early termination/withdrawal will be summarized.

Compliance and Exposure

Participant exposure will be presented including number of treatments received and duration of treatment. Duration of treatment will be calculated in weeks as follows:

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 13 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

Last dose date – First dose date + 2 weeks

6.2 Efficacy Analysis

Will be performed on the Treated population for the final analysis.

Overall Response Rate (ORR) is defined as the proportion of population of interest whose Best Overall Response (BOR) is either Complete Response (CR) or Partial Response (PR) per RECIST v1. Estimate of ORR and corresponding 2-sided exact 95% CI will be calculated based on the Clopper-Pearson method. The analysis will be performed by dose cohort as well and repeated for each tumor type with an appropriate sample size.

Disease Control Rate (DCR) is defined as the proportion of population of interest whose BOR is either CR, PR or Stable Disease (SD) per RECIST v1. The analysis will be performed by dose cohort as well and repeated for each tumor type with an appropriate sample size.

Median Duration of Response (DoR) will be calculated using the Kaplan-Meier method (K-M) with a corresponding 2-sided 95% CI (using transformation as appropriate). Duration of response 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. DoR will be censored at the last follow-up time if a patient is still alive at the time of last follow up. The analysis will be performed by dose cohort as well and repeated for each tumor type with an appropriate sample size.

Median Progression Free Survival (PFS) will be calculated using the Kaplan-Meier method (K-M) with a corresponding 2-sided 95% CI (using transformation as appropriate). The analysis will be performed by dose cohort as well and repeated for each tumor type with an appropriate sample size.

PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. PFS will be censored at the last follow-up time if a patient is still alive at the time of last follow up.

PFS rate at 3, 6, 9, 12 months, and up to 24 months per RECIST v1.1 will be calculated based on the Clopper-Pearson method for each tumor type corresponding 2-sided exact 95% CI will be calculated as well. The analysis will be performed by dose cohort as well and repeated for each tumor type with an appropriate sample size.

Pooled efficacy analysis for group specific dose level cohorts may be explored.

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 14 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

6.3 Safety analysis

Safety data will be summarized for the Treated population. A separate table will present SAEs related to screening procedures.

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.

The number and percentage of participants reporting AEs, SAEs, study drug-related AEs and AEs leading to drug discontinuation will be summarized.

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.

The following by-treatment summaries will be generated separately for hematology, biochemistry, coagulation, and urinary laboratory tests:

In addition to relative changes from baseline summaries, shift table using normal/low NCS/high NCS/low CS/high CS classification to compare baseline to the worst category by cycle. (shift tables using CTCAE grade may be considered for the expansion phase). If there are two symmetric worst categories in the same cycle, i.e. low NCS and high NCS or low CS and high CS, it will be coded respectively as abnormal NCS or abnormal CS with an explicative footnote.

Listing of all laboratory data with values flagged to show the corresponding classifications relative to the laboratory normal ranges.

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.

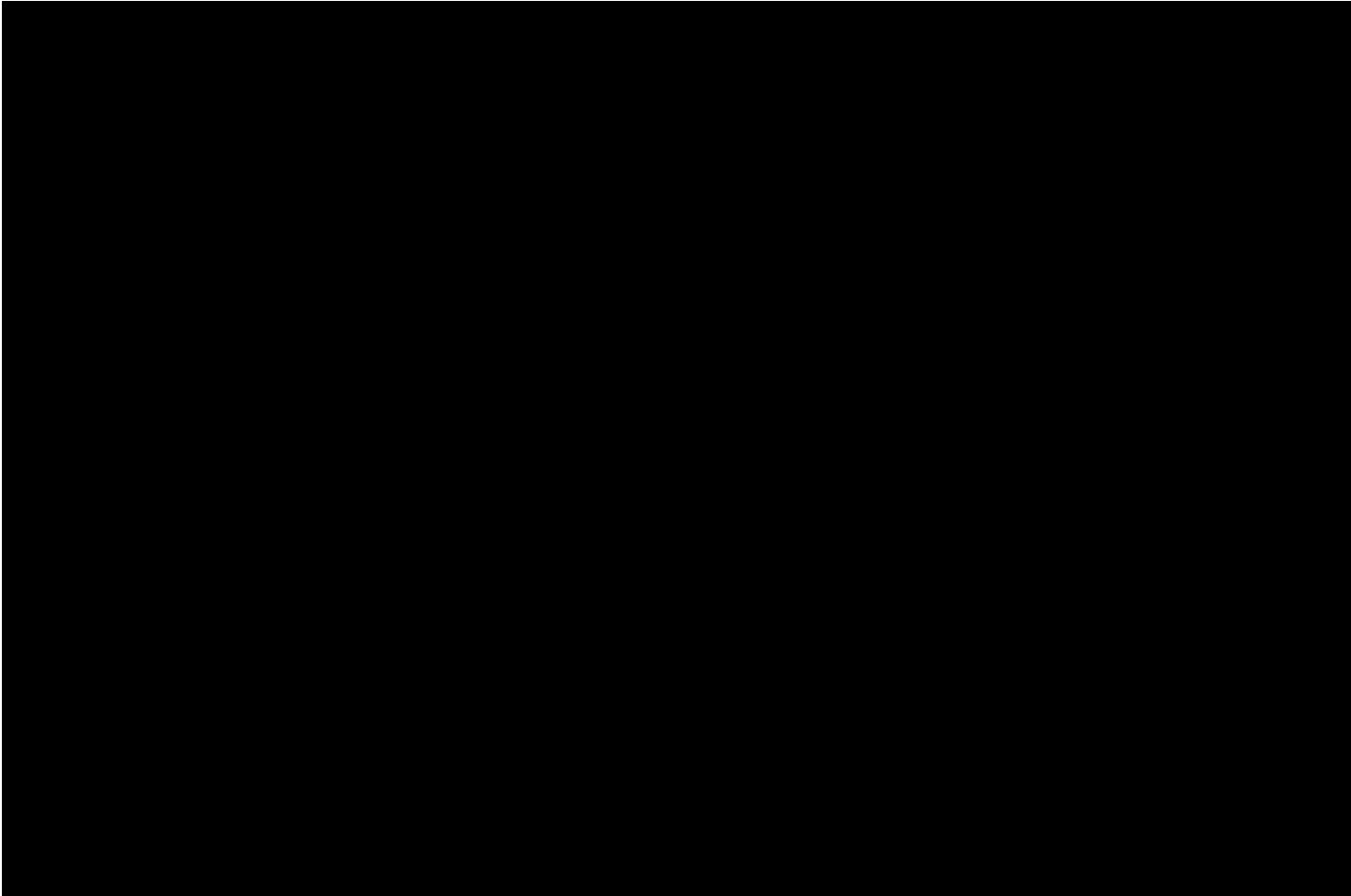
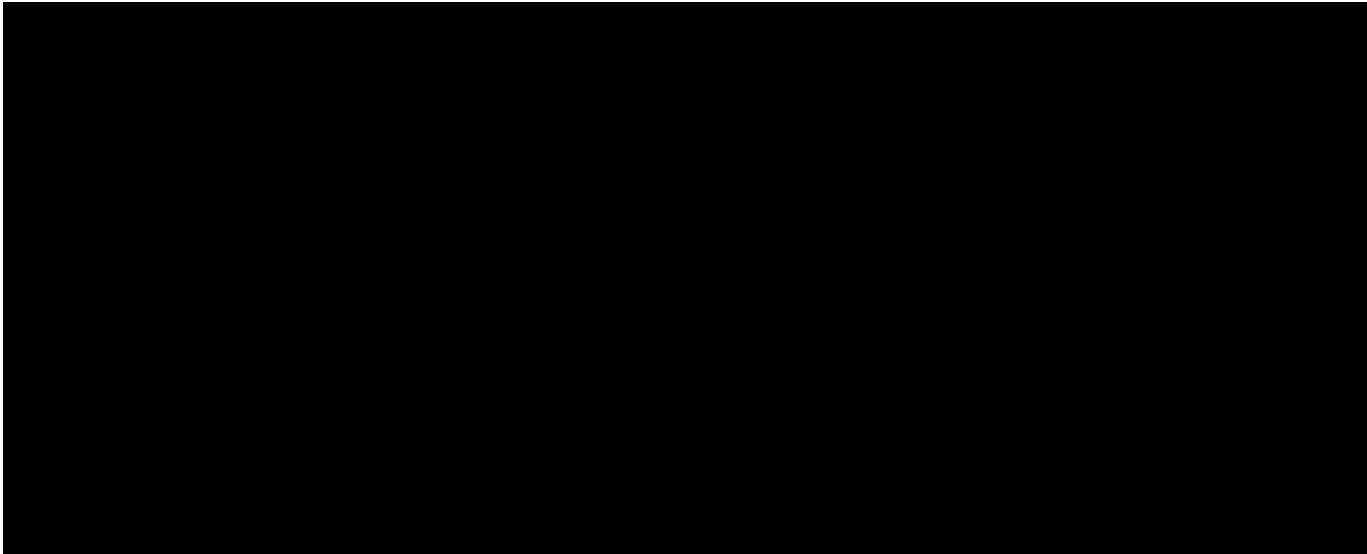
Analysis of vital signs will include a table with descriptive statistics at baseline and post-baseline time points and relative change from baseline to these post-baseline time points.

Abnormal physical examination findings will be presented in a by subject data listing.

Concomitant medication verbatim terms (as recorded on the CRFs) will be coded to Anatomical Therapeutic Chemical (ATC) Level 2 and 4 using the World Health Organization (WHO) dictionary. Summary by ATC will be presented.

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 15 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

6.4 Exploratory analysis



	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 16 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : 30/NOV/2023 REVISION NUMBER : 3.0

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7. RELATED DOCUMENTS

7.1 Study protocol: TCD17465 Clinical Protocol Version 5_2.docx

8. RELATED FORMS

Not Applicable

9. APPENDICES

9.1 Appendix I: BND_BND-22-001_BS_SAP Appendix I_V3.pdf

9.2 Appemdix II: BND_BND-22-001_BS_SAP Appendix II_V3.pdf

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 17 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : [REDACTED] REVISION NUMBER : 3.0

10. SIGNATURE PAGE

Author

Name: [REDACTED]

Position: [REDACTED]

Company: Medistat Ltd.

Date: [REDACTED]

[REDACTED]

Reviewer

Name: [REDACTED]

Position: [REDACTED]

Company: Medistat Ltd.

Date: [REDACTED]

[REDACTED]

Update to version 2.0

Name: [REDACTED]

Position: [REDACTED]

Company: Medistat Ltd.

Date: [REDACTED]

[REDACTED]

Update to version 3.0

Name: [REDACTED]

Position: [REDACTED]

Company: Medistat Ltd.

Date: [REDACTED]

[REDACTED]

	DOCUMENT NUMBER: BND_BND-22-001_BS_SAP	PAGE: 18 of 18
TITLE: Statistical Analysis Plan for BND-22-001 Sub-Part 1A		EFFECTIVE DATE : [REDACTED] REVISION NUMBER : 3.0

Approved by

Name:

Position:

Company: Biond Biologics Ltd.

Date:

STATISTICAL ANALYSIS PLAN

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)
Compound number (INN/Trademark):	SAR444881 (formerly BND-22) Not applicable
Study phase:	Phase 1/Phase 2
Short Title:	Study of SAR444881 administered alone and in combination with other therapeutics in participants with advanced solid tumors
Statistician:	
Statistical project leader:	
Date of issue:	13-Jun-2024
Regulatory agency identifier number(s):	
IND:	145335
EudraCT:	2023-504937-30
NCT:	NCT04717375
WHO:	Not applicable
EUDAMED:	Not applicable
Other:	Not applicable

Date:	13-Jun-2024	Total number of pages: 70
-------	-------------	---------------------------

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN	1
TABLE OF CONTENTS	2
LIST OF TABLES	5
LIST OF FIGURES	5
VERSION HISTORY	6
1 INTRODUCTION	10
1.1 STUDY DESIGN	10
1.2 OBJECTIVE AND ENDPOINTS	17
2 ANALYSIS POPULATIONS	18
3 STATISTICAL ANALYSES	20
3.1 GENERAL CONSIDERATIONS	20
3.2 PRIMARY ENDPOINT(S) ANALYSIS	21
3.2.1 Definition of endpoint(s)	21
3.2.1.1 Best overall response	21
3.2.2 Main analytical approach	23
3.3 SECONDARY ENDPOINT(S) ANALYSIS	23
3.3.1 Key/Confirmatory secondary endpoint(s)	23
3.3.1.1 Definition of endpoint(s)	23
3.3.1.2 Main analytical approach	26
3.3.2 Supportive secondary endpoint(s)	26
3.3.2.1 Definition of endpoint(s)	26
3.3.2.2 Main analytical approach	27
3.4 [REDACTED]	28
3.5 MULTIPLICITY ISSUES	28
3.6 SAFETY ANALYSES	28
3.6.1 Extent of exposure	28
3.6.1.1 Overall exposure	29
3.6.1.2 SAR444881, Pembrolizumab, Cetuximab, Pemetrexed and Carboplatin exposure	30
3.6.2 Adverse events	33
3.6.3 Additional safety assessments	38
3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)	38

3.6.3.2	Physical examination	40
3.6.3.3	Left ventricular ejection fraction and troponin	40
3.7	OTHER ANALYSES.....	41
3.7.1	Other variables and/or parameters	41
3.7.1.1	PK analyses	41
3.7.1.2	Immunogenicity analyses.....	42
3.7.1.3	Quality of life analyses	43
3.7.1.4	Biomarker analyses.....	44
3.7.1.5	Other PK/PD analyses	44
3.8	INTERIM ANALYSES	44
3.8.1	Safety Review Committee.....	44
3.8.2	End of safety-run in for Cohort A1	45
3.8.3	Continuous evaluation of toxicity	46
3.8.4	Interim analysis at the end of Stage 1 of each cohort.....	47
3.8.5	Primary analysis at the end of Stage 2 of each cohort	47
3.9	CHANGES TO PROTOCOL-PLANNED ANALYSES.....	47
4	SAMPLE SIZE DETERMINATION	49
4.1	DOSE OPTIMIZATION/EXPANSION	49
5	SUPPORTING DOCUMENTATION	50
5.1	APPENDIX 1 LIST OF ABBREVIATIONS	50
5.2	APPENDIX 2 TWO-STAGE DESIGN	53
5.2.1	Two-stage design.....	53
5.2.2	Simulation study.....	55
5.3	APPENDIX 3 PARTICIPANT DISPOSITIONS	57
5.4	APPENDIX 4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS	59
5.5	APPENDIX 5 DATA HANDLING CONVENTIONS	61
5.5.1	Analysis windows for time points	61
5.5.2	Unscheduled visits	61
5.5.3	Analysis cut-off date.....	61
5.6	APPENDIX 6 TUMOR RESPONSE ASSESSMENT	62
5.6.1	Evaluation of lesions	62
5.6.1.1	Measurable lesions	62
5.6.1.2	Non-measurable lesions	63
5.6.1.3	Bone lesion measurability	63

5.6.1.4	Baseline documentation of target and non-target lesions.....	63
5.6.2	Response criteria	64
5.6.2.1	Evaluation of target lesions.....	64
5.6.2.2	Special Notes on the Assessment of Target Lesions	64
5.6.3	Evaluation of non-target lesions.....	65
5.6.3.1	Special notes on assessment of progression of non-target disease	65
5.6.3.2	New lesions.....	66
5.6.4	Response assessment.....	67
5.6.4.1	Time point response.....	67
5.6.5	Reasons for Responses.....	68
6	REFERENCES.....	70

LIST OF TABLES

Table 1 – Overview of study cohorts	11
Table 2 - Objectives and endpoints: optimization/expansion (Part 2)	17
Table 3 - Populations for analyses	18
Table 4 - Best overall response (confirmation of CR and PR required)	21
Table 5 - Event and censoring definitions for PFS	24
Table 6 - Frequency of dosing and cycle duration for study medication	30
Table 7 - Cetuximab dose reduction criteria	31
Table 8 - Pemetrexed dose reduction criteria	32
Table 9 - Carboplatin dose reduction criteria	32
Table 10 - Sorting of AE tables	34
Table 10 - Analyses of adverse events	36
Table 12 - Selections for other AEs of interest	38
Table 13 - List of PK parameters and definition	41
Table 14 - Bayesian toxicity monitoring plan in dose optimization/expansion phase	47
Table 15 - Major statistical changes from protocol amendment 12	47
Table 16 – Estimated ORR and 95% CI	49
Table 17 - Reference and target ORRs for each indication	55
Table 18 - [REDACTED]	56
Table 19 - [REDACTED]	56
Table 20 - [REDACTED]	57
Table 21 - Time point response: patients with target (± non-target) disease	67
Table 22 - Time point response: patients with non-target disease only	68

LIST OF FIGURES

Figure 1 – Study design schematic	13
Figure 2 – Overall design for dose optimization/expansion	14
Figure 3 – Schematic for study periods and participant flow for Part 2 Cohorts C1, D1, and E1	15
Figure 4 – Schematic for study periods and participant flow for Part 2 Cohorts A1 and B1	16
Figure 5 - The two-stage design schema with hypothetical two GO and two No-Go of indications after Stage 1	54

VERSION HISTORY

This statistical analysis plan (SAP) for study TCD17465 (formerly BND-22-001) is based on the protocol dated 13-May-2024 and covers the dose optimization/expansion part of this study. There is a separate SAP for the dose escalation phase of the study.

The first participants in the dose escalation and dose optimization/expansion parts were enrolled on 14 April 2021 and 9 February 2024, respectively. The original version of the SAP was approved before the first participant was enrolled into the dose optimization/expansion part. The SAP is amended after a protocol amendment and this amended version of the SAP is approved before the first interim analysis is conducted in the dose optimization/expansion part.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.3	29-Mar-2024	Throughout the document sections relating to the study design for Part 1 of the study were removed as this SAP is for Part 2 only. Throughout the document, Cohort A2 was removed and Cohort E1 was added per the protocol amendment. Changes to the study design (Section 1.1) were made per the changes in the protocol amendment. In Section 2 the Intention-to-treat population definition was updated to remove "and planned dose level (if applicable)" as all participants would be randomized in this population, so this text is not relevant. In Section 2 the response-evaluable population was removed as this is no longer used in the planned analyses. This is a change from the current protocol but may be updated in a future amendment to the protocol (see Section 3.9). The summary of analyses performed in Part 2 were removed from Section 3.1 as these are covered later on in the document. Clarification was added to Section 3.1 for the baseline definition to specify the handling of time in selecting the baseline value and to further clarify that the reference start date is the date of first dose of IMP. Details of the populations used for each endpoint were removed from Section 3.1 as this is covered in each Section defining the analyses. The treatment emergent period was updated to use the last IMP administration + 30 days rather than + 90 days to reflect the standard definition for the follow up period after last dose. In Section 3.1 the on-treatment period was changed to have the same definition as the treatment emergent period. Text was removed from the start of Section 3.2 that outlines the data to be used as part of the optimal dose determination. Section 3.2.1 (including the subsections) was restructured but the definitions of BOR and ORR remained the same. Details on the reasons for response were moved from Section 3.2.1.1 to Appendix 6 Section 5.6.5 and the text was restructured but the reasons remained the same.	Protocol Amendment, FDA feedback, clarifications, simplification of text

SAP Version	Approval Date	Changes	Rationale
		In Section 3.2.2 the ORR was updated to be summarized in the treated rather than the response-evaluable population. This is a change from the current protocol where the analysis population for ORR at the interim analysis is specified to be the response-evaluable population. This is in response to FDA guidance that additional restrictions should not be added for ORR analyses to avoid an overestimate of the response rate. This may be updated in a future amendment to the protocol (see Section 3.9). In Section 3.3 the reference to RECIST v1.1 in Section 5.7 was removed. In Section 3.3.1.1.2 additional clarification on the minimal protocol specified duration between first dose of IMP and SD was added to the definition of DCR. Additional clarification was added to Section 3.3.1.1.3 to clarify the definition of the date of the first confirmed CR/PR and to include clarification on the minimal protocol specified duration between first dose of IMP and SD. Survival rates were added to Section 3.3.1.2.3 for DoR and DoR was updated to be summarized in the treated population rather than the response-evaluable population to be in line with ORR. In Sections 3.3.2.1.1 and 3.3.2.2.2 the time to response was split into time first response and time to best response. Current Section 3.3.2.1.3 had minor updates to only specify the data included in the derivations in one place, but the definition remains unchanged. In Section 3.3.2.2.1 time to response was updated to be summarized in the treated population rather than the response-evaluable population to be in line with ORR Current Section 3.3.2.2.3 was simplified and best percentage change was updated to be summarized in the treated population rather than the response-evaluable population to be in line with ORR. Section 3.4 was updated to reference the relevant sections for each endpoint. Clarification was added to Section 3.6.1.1 that this section considers all study medications and that the groups by cycle relate to cohorts with 28-day cycles and cohorts with 21-day cycles. In Section 3.6.1.2 clarification was added to cover the different units for the different study interventions. Table 6 was added to Section 3.6.1.2 to summarize key aspects for the exposure in the different cohorts. In Section 3.6.1.2 summaries of the number of participants, cycles and infusions with dose reductions for cetuximab, pemetrexed and carboplatin were included. Some minor changes were made to Section 3.6.1.2 to simplify the text. In Section 3.6.2 clarification that possibly related would be included as related was added. A definition of permanent partial intervention discontinuation was added to Section 3.6.2. In Section 3.6.2 the summary of deaths in non-randomized/non-enrolled participants or randomized/enrolled but not treated participants was removed.	

SAP Version	Approval Date	Changes	Rationale
		The definition of permanent discontinuation of study medications was updated to include both partial and full discontinuations for each individual study medication in Cohorts where a combination is to be administered. In Section 3.6.1.2 reference to AESIs was removed from current Table 11. Quantitative analyses of laboratory values by visit were removed from Section 3.6.3.1 as these are not produced when local laboratory data are used. In Section 3.6.3.1, the summary of abnormal laboratory values during the treatment-emergent period were removed. Listings of laboratory data were removed from Section 3.6.3.1. This is a change from the analysis per protocol. In Section 3.6.3.1, the liver function test summary tables were replaced with newer standard tables. The time to onset of ALT, AST and bilirubin elevations Kaplan-Meier plot was removed from Section 3.6.3.1. In Section 3.7.1.1 the plots of PK data were updated to present arithmetic rather than geometric means and clarification was added that this would include a line per dose level. The sample status and titers over time summary tables for anti-drug antibody data were removed from Section 3.7.1.2. In Section 3.7.1.2 the definition of treatment-boosted ADAs was updated to clarify how this will be handled for 4- and 3- fold serial dilution schema. Additional clarification was added for the definition of inconclusive ADA in Section 3.7.1.2. Summary of participants with ADAs directed against a specific domain was removed from Section 3.7.1.2. Details were added to Section 3.7.1.2 was added for summarizing of the time to onset of ADA response. Clarification around handling positive samples at least 16 weeks apart were removed from Section 3.7.1.2. Clarification was added for the definition of indeterminate ADA response in Section 3.7.1.2. A summary table was added for quality of life data to Section 3.7.1.3 as was details on the methods of summarizing these data. The listing of biomarker data was removed from Section 3.7.1.4. Reference to the PK/PD analysis plan was removed from Section 3.7.1.5. Clarification was added to Section 3.8 to specify that the end of the cohort refers to the end of Stage 2. Section 3.8.2 was updated based on the protocol amendment. The summary of the TEAEs by CTCAE grade, SOC and PT and the plot of incidence of TEAEs related to study drug were removed from the list of tables and figures to be presented for the SRC review of data. This is a change from the SRC charter. Section 5.2 was updated with the changes in the protocol amendment, however, the combination therapy for the Herbst et al. reference was left as SAR444881 + pembrolizumab as this is the combination therapy from the reference paper. This differs from the corresponding table in the protocol.	

SAP Version	Approval Date	Changes	Rationale
		A swimmer plot was added to current Section 5.3. In current Section 5.3 the summary of protocol deviations was updated to be in the treated population and clarification was added to describe the method of identifying the protocol deviations. In current Section 5.4 demographics and baseline characteristics were updated to be presented in the treated population. Clarification on the collection/derivation of BMI and BSA was added to Section current Section 5.4. In current Section 5.4 clarification was added that surgical history will come from the prior procedures eCRF page. Clarification on the derivation of the time to initial diagnosis was added to current Section 5.4 and this was updated to use the date of first dose rather than the randomization/enrolment date. In current Section 5.4, the summary of prior, concomitant and post-treatment medications in the enrolled population was removed. Summary of Child-Pugh scoring, albumin-bilirubin score, model for end stage liver disease score and toxicity or allergy related to previous treatment were removed from current Section 5.4. Clarification on the derivation of the time from most recent progression to treatment was included and this was updated to use the date of first dose rather than the randomization/enrolment date I current Section 5.4. Clarification was added to current Section 5.4 that the intent and response to most recent therapy would be summarized and that the line number would be presented for metastatic/locally advanced therapy.	
1	19-Dec-2023	In Section 11.3.1 of protocol version 6, the efficacy analyses are planned in the treated population. For the objective response rate (ORR) and duration of response (DoR), the endpoints will be summarized in the response-evaluable population. In Section 2.3.3 of Appendix 7 of protocol version 6, the minimum time for the response of stable disease (SD) is taken from the date of first treatment or randomization date is updated to the date of first intake of IMP to align with all other endpoints derived based on tumor assessments.	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This is an open-label, multicenter, Phase 1/2, first-in-human study of intravenous SAR444881, a humanized monoclonal immunoglobulin G4 (IgG4) antibody, targeting the immunoglobulin-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 human leukocyte antigen G (HLA-G). Tumor types included in SAR444881-cetuximab combination cohorts are tumors known to over-express the epidermal growth factor receptor (EGFR) protein.

This study is comprised of two parts: a dose escalation phase (Part 1) and a dose optimization/expansion phase (Part 2). This SAP covers the statistical analyses for the dose optimization/expansion phase (Part 2). There is a separate SAP for the dose escalation phase (Part 1).

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 (PoC) that combining SAR444881 as a monotherapy or in combination with one or more of the following: 1) the anti-programmed death protein 1 (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) and in Sub-Part 2B, the preliminary anti-tumor activity of SAR444881 is assessed as a monotherapy.

The purpose of the SAR444881 dose optimization (Sub-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 to gather additional safety, tolerability, PK, and PD information in order to define the optimal dose of SAR444881. The purpose of the SAR444881 dose expansion (Sub-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. The indications under investigation are described in [Table 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 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 2L and later therapy	CRC any RAS
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 gastroesophageal junction adenocarcinoma; CRC: colorectal carcinoma; RAS: rat sarcoma.

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, pharmacokinetic (PK), and pharmacodynamic (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. In addition to efficacy/safety data obtained from Stage 1, initiation of Stage 2 of Sub-Part 2A for any given indication will take into account the totality of all data obtained from all indications in Part 2 as well as data obtained from Part 1. 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 Safety Review Committee (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.

More details of two-stage design are detailed in [Section 5.2](#).

Part 2 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 of the protocol.

An interim analysis (IA) will be performed at the end of Stage 1 to determine if the Cohort should continue onto Stage 2 (see [Section 3.8.4](#) for more details on the IA).

In Stage 1 of Sub-Part 2B, the efficacy of SAR444881 monotherapy will be evaluated in 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.

For Stage 2, based on preliminary assessment of totality of data at the end of Stage 1, one of the following three scenarios will be proposed: 1) randomize n=40 patients 1:1 to one of two dose levels; 2) add an additional 20 patients at the same dose level tested in Stage 1 (i.e., no randomization). 3) close the cohort.

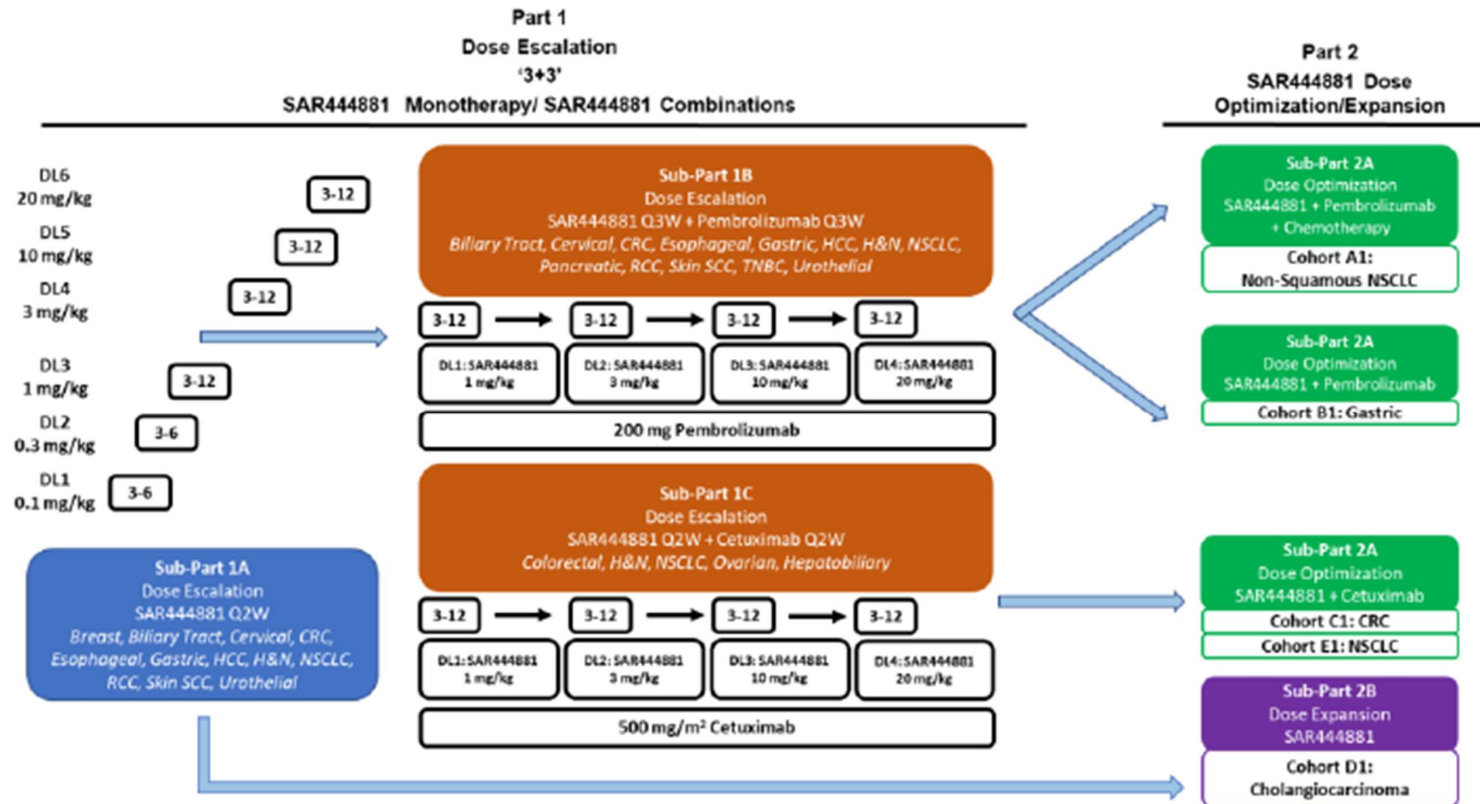
In Cohort A1 (SAR444881 + pembrolizumab + carboplatin + pemetrexed) for non-squamous NSCLC there is a safety run-in and a core phase. Participants who fulfill the eligibility criteria of any cohort testing the regimen may be enrolled to the safety run-in of that regimen. The initial SAR444881 dose tested in the safety run-in for Cohort A1 will be 10 mg/kg (see [Section 3.8.2](#) for more details).

Continuous evaluation of toxicity events will be performed throughout enrollment for all optimization/expansion cohorts (see [Section 3.8.3](#) for more details on the continuous evaluation of toxicity events).

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).

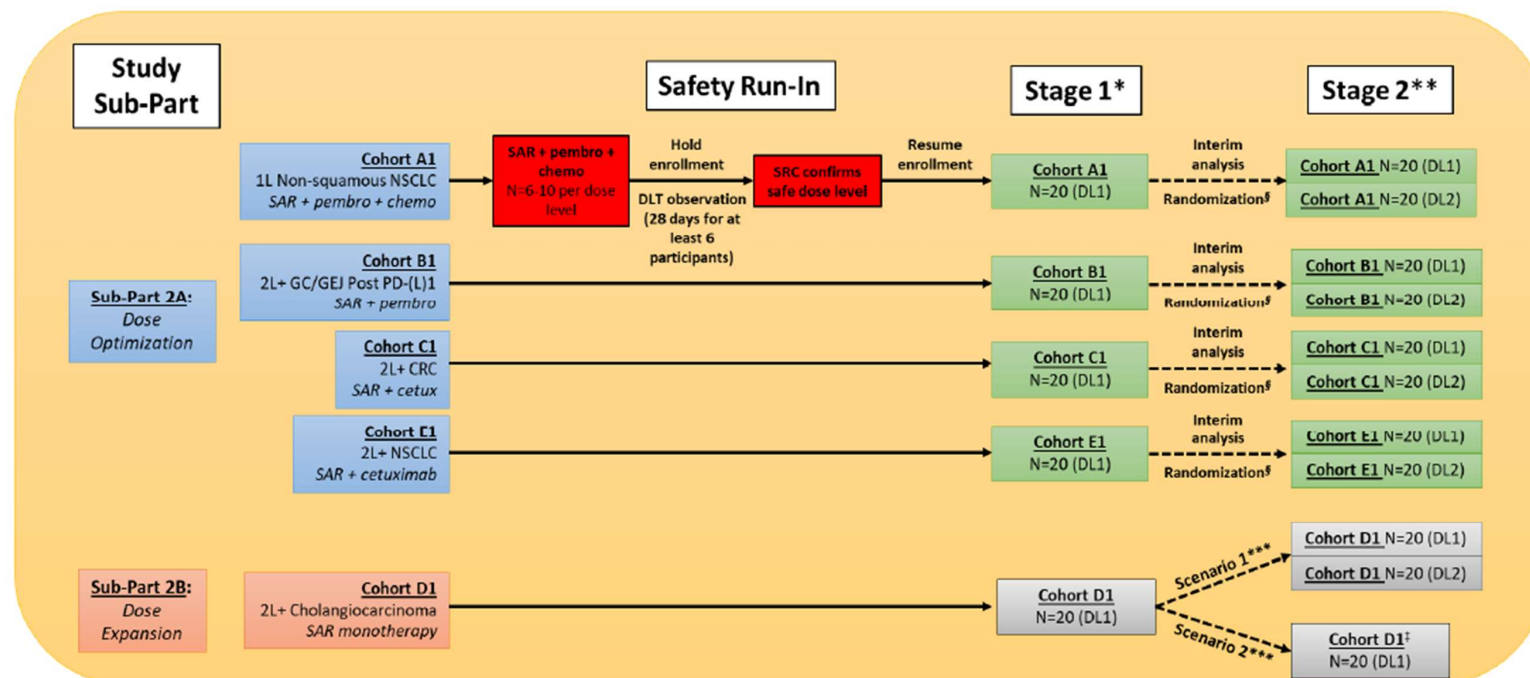
A schematic for study periods and participant flow is presented in [Figure 3](#) for Cohorts C1,D1, and E1, and [Figure 4](#) for Cohorts A1 and B1.

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; Q2W: every 2 weeks; Q3W: every 3 weeks; RCC: renal cell carcinoma; SCC: squamous cell carcinoma; TNBC: triple negative breast cancer.

Figure 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. ***Scenario 1 – favorable efficacy in Stage 1 warrants randomization in Stage 2; Scenario 2 – marginal efficacy in Stage 1 warrants adding an additional 20 participants but no randomization.

1L = first line; 2L+ = second line or later; DLT: dose limiting toxicity; NSCLC = non-small cell lung cancer; GC/GEJ = gastric cancer or gastroesophageal junction adenocarcinoma; CRC = colorectal carcinoma; cetux: cetuximab; chemo: chemotherapy (carboplatin/pemetrexed); pembro: pembrolizumab; SRC: Safety Review Committee; SAR: SAR444881; DL: dose level; TBD: to be determined.

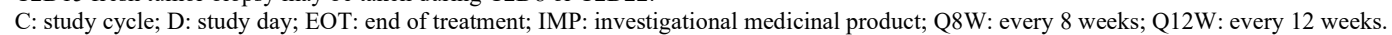
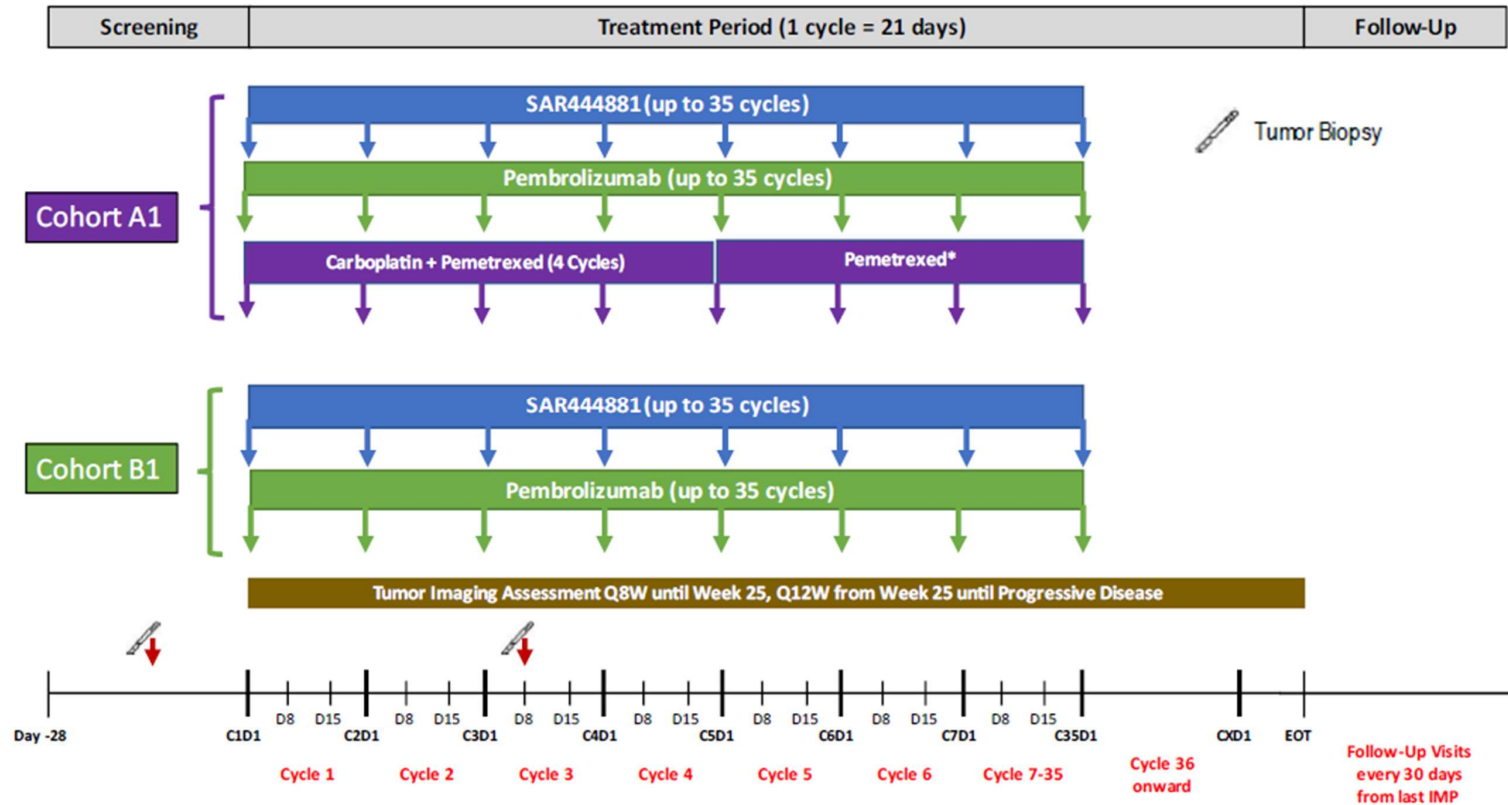


Figure 4 – Schematic for study periods and participant flow for Part 2 Cohorts A1 and B1



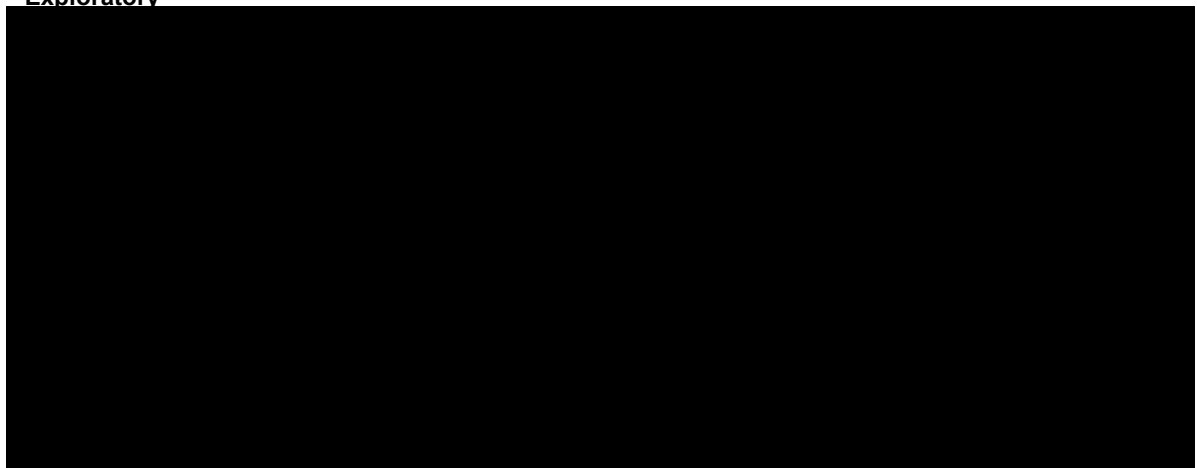
*Pemetrexed to be administered until progressive disease, intolerability, withdrawal of consent, or initiation of another systemic anti-cancer treatment.
C: study cycle; D: study day; EOT: end of treatment; IMP: investigational medicinal product; Q8W: every 8 weeks; Q12W: every 12 weeks.

1.2 OBJECTIVE AND ENDPOINTS

Table 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. Objective response rate (ORR) per RECIST v1.1 [other datapoints may be utilized to supplement assessment of optimal SAR444881 dose, the optimal dose will be based on the totality of data including efficacy, safety, pharmacokinetics/pharmacodynamics (PK/PD) and biomarkers].
Secondary	
1. To assess additional parameters of antitumor 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. Progression-free survival (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 (PFSR) at 3, 6, 9, 12 months, and up to 24 months per RECIST v1.1; disease control rate (DCR); duration of response (DoR) defined as the duration between first documentation of complete response (CR) or partial response (PR) to first documentation of disease progression or death from any cause, whichever occurs first. 2. Incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs), as described above. 3. PK parameters of SAR444881 [maximum observed concentration (C_{max}), concentration at the end of the dosing level (C_{trough}), time reach to maximum concentration (T_{max}), half-life ($T_{1/2}$), area under the curve (AUC)]. 4. Incidence of anti-drug antibodies (ADA), including neutralizing ADA (nADA), to SAR444881.

Exploratory



2 ANALYSIS POPULATIONS

The following populations for analyses are defined. Data from the dose optimization/escalation part of the study will be presented separately for each cohort by dose level of SAR444881. Participants treated at the same dose level of SAR444881 in Stages 1 and 2 in each cohort will be summarized together and will not be presented by Stage. Similarly, participants enrolled into the safety run-in of Cohort A1 will be presented with other participants enrolled in the core phase of Cohort A1 who are treated at the same dose level of SAR444881 and will not be presented separately.

Unless otherwise stated, data from participants treated at different dose levels of SAR444881 or enrolled into different cohorts will not be combined and summarized as a total. Data from different cohorts may be presented side-by-side for the clinical study report (CSR).

Table 3 - Populations for analyses

Population	Description
Enrolled	All participants who sign informed consent.
Intention-to-treat (ITT)	All participants who sign informed consent and for whom there is confirmation of successful allocation of a randomization number by the interactive response technology (IRT). Participants will be analyzed according to the treatment arm assigned at randomization.
Treated	All participants who receive at least 1 dose of study treatment. For cohorts in Sub-Part 2A where a combination of study treatments is to be administered, participants will be considered to have received at least 1 dose of study treatment if the participant receives at least 1 dose of SAR444881 in Sub-Part 2A. Participants will be analyzed according to the dose level of SAR444881 they actually received with the exception of efficacy data. Participants will be analyzed according to the treatment arm assigned at randomization and planned dose level (if applicable) for efficacy data.
Pharmacokinetic (PK)	All treated participants who have evaluable concentration-time data (with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times). Participants will be analyzed according to the dose level of SAR444881 they actually received.
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline pre-infusion immunogenicity assessment with an ADA result (positive, negative or inconclusive). Participants will be analyzed according to the dose level of SAR444881 they actually received.
Biomarker	All treated participants with available biomarker data. Participants will be analyzed according to the dose level of SAR444881 they actually received.

Participants exposed to study intervention before or without being enrolled/randomized will not be considered enrolled/randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Enrolled/randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the treated population as randomized or at the planned dose level.

Participants can only be re-enrolled if the participant discontinued the study as a pre-treatment failure. Re-enrolled participants will not be given a new subject number. Retesting of laboratory parameters and/or other assessments within any single screening period is permitted and the new result will override the previous result for assessing study inclusion.

Dose reductions or increases are not allowed in Part 2 for SAR444881 per the protocol and therefore the actual SAR444881 dose received is expected to be as planned/randomized. However, for participants receiving at least one dose of SAR444881 that is not the planned/randomized dose level for that participant during the study, then their actual dose level will be assigned as follows:

- If the participant receives only one dose level, then they will be included in the dose level group of their actual dose level received.
- If the participant received multiple dose levels during the study:
 - If the participant receives at least 1 dose as planned/randomized, then they will be included in the dose level group as planned/randomized for their actual dose level.
 - If the participant does not receive any dose at the planned/randomized dose level, but they receive at least 1 dose that is planned for other participants within that cohort, then the participant will be included in the dose level group of their actual dose level received.
 - If the participant does not receive any of the planned/randomized dose levels used in the Cohort, then they will be included in a dose level group of their actual dose level received at C1D1.

Assignment of actual treatment will be reviewed at the participant level prior to database lock to ensure that the assignments are appropriate. In the by-participant listings, the last doses of study medication will be presented for adverse events (AEs).

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

The analysis cut-off date (COD) for each cohort at the end of Stage 2 will be the date approximately 9 months after the last participant's last dose of study medication in the cohort or early discontinuation of all study medication, whichever comes first. The overall study analysis COD will be when the last cohort has reached its analysis COD (see [Section 5.5.3](#) for details on the application of a COD for analysis).

In general, continuous data will be summarized using the number of observations available, mean, standard deviation, median, upper quartile (Q1), lower quartile (Q3), minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The investigational medicinal product (IMP) differs between cohorts and, unless otherwise stated, IMP refers to any study medication (SAR444881, pembrolizumab, cetuximab, carboplatin and pemetrexed) to be administered in the specified cohort throughout this document.

The reference start date will be the date of first dose of IMP (Day 1), unless otherwise specified. This applies for all participants who are treated, including those randomized to different doses as part of Stage 2 of a given cohort.

For all participants, including participants who are randomized as part of Stage 2, and for all analyses, including efficacy, the baseline value is defined as the last available value before the first dose of IMP. For participants randomized but not treated, the baseline value is defined as the last available value before randomization. If the times are collected, then the time is used to determine if a value is before the first dose of IMP. If the time is missing and the assessment is scheduled to be collected prior to first dose of IMP per the protocol, then the value will be assumed to be before first dose of IMP if the date is on or before the date of first dose of IMP. For example, for vital signs data collected in Cohort B1:

- If a patient receives pembrolizumab first, the planned time point is pre-infusion on the eCRF for "vital signs – pembrolizumab" and the vital signs data are collected on the date of first dose of pembrolizumab, then these vital signs data are included in the derivation of the baseline assessment.
- If a patient receives pembrolizumab first, the planned time point is pre-infusion on the eCRF for "vital signs – SAR444881" and the vital signs data are collected on the date of first dose of study medication, then these vital signs data are not included in the derivation of the baseline assessment as this is scheduled to be taken after pembrolizumab.
- If a patient receives SAR444881 first and does not receive pembrolizumab, the planned time point is pre-infusion on the eCRF for "vital signs – SAR444881" and the vital signs data are collected on the date of first dose of study medication, then these vital signs data are included in the derivation of the baseline assessment.

Unless otherwise specified, analyses will be performed separately for dose escalation and dose optimization/expansion.

- In the dose optimization/expansion part, unless otherwise specified, analyses will be performed separately for each cohort by dose level of SAR444881. Data will not be presented by stage and data from the safety run-in of Cohort A1 will not be presented separately from data collected for participants dosed at the same dose level of SAR444881 in the core phase of Cohort A1.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The on-treatment period (ie, **treatment-emergent (TE) period**) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the period from the end of the TE period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint detailed in this section is the ORR.

3.2.1 Definition of endpoint(s)

Objective response rate is defined as the proportion of participants in the population of interest with a best overall response (BOR) of either CR or PR that is confirmed at least 4 weeks later. Details on the derivation of the BOR and confirmation of response are given in [Section 3.2.1.1](#). Participants in the specified population of interest who do not meet the criteria for a BOR of CR or PR will be included in the denominator as non-responders.

3.2.1.1 Best overall response

Overall responses, which are CR, PR, SD, PD and NE, will be evaluated from the first start date of study treatment to the date of documented disease progression, death, start of an anti-cancer therapy or COD, whichever occurs first. Anti-cancer therapies will be identified from the data collected on the “Subsequent Anti-cancer Drug Therapies” eCRF page. According to the RECIST 1.1 criteria, overall response will be reported by the Investigator assessment in the eCRF. Tumor assessments performed on the same day as the start of an anti-cancer therapy will be considered for the derivation of the BOR.

The BOR is based on the confirmed response as shown in [Table 4](#) below:

Table 4 - 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 provided minimum criteria for SD, PD or PR ^a

Overall response first time point	Overall response subsequent time point	Best overall response
CR	SD (or Non-CR/non-PD)	SD (or Non-CR/non-PD) provided minimum criteria for SD (or Non-CR/non-PD) duration met, otherwise, PD
CR	PD	SD (or Non-CR/non-PD) provided minimum criteria for SD (or Non-CR/non-PD) duration met, otherwise, PD
CR	NE	SD (or Non-CR/non-PD) provided minimum criteria for SD (or Non-CR/non-PD) duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD (or Non-CR/non-PD)	SD (or Non-CR/non-PD)
PR	PD	SD (or Non-CR/non-PD) provided minimum criteria for SD (or Non-CR/non-PD) duration met, otherwise, PD
PR	NE	SD (or Non-CR/non-PD) provided minimum criteria for SD (or Non-CR/non-PD) duration met, otherwise, NE
NE	NE	NE

CR: complete response; NE: not evaluable; PR: partial response; PD: progressive disease; SD: Stable disease.

^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.

A BOR of CR or PR may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. 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 intervening time point will be allowed between PR/CRs for confirmation. A participant with the following sequence of overall response will not be considered as having a confirmed response: PR – NE – NE – PR is considered as SD or Non-CR/Non-PD, until further confirmation of the 2nd PR.

For a BOR of SD, any best response of SD must meet the protocol specified minimum time of at least 49 days from the date of first dose of IMP (49 days represents the time to the first imaging visit at Week 8 or 56 days – the 7-day visit window). The date of first dose of IMP represents Day 1. If the participant is not on-study for at least this amount of time, any tumor assessment indicating SD before this time period will have a Best Response of NE, unless the criteria for PD is met.

If the participant dies due to PD (per the death eCRF page) between the first IMP intake and the planned date of the 2nd tumor assessment (including the allowed window period), the BOR will be PD and the date of PD will be the date of death.

An evaluable tumor assessment is defined as a tumor assessment with an overall response different from NE.

Best overall response will be set to NE in the following situations:

- The participant has a best response of SD that does not meet the protocol specified minimum time of at least 49 days after first dose of IMP.
- No baseline or post-baseline tumor assessment is available and the participant does not have a death that meets the criteria for a BOR of PD outlined above.
- The only evaluable assessment has an overall response of PD and the time between the date of first intake of any IMP and the documentation of PD is greater than 17 weeks after the first dose of IMP (after the theoretical planned date of the 2nd tumor assessment including the allowed time window period for tumor assessment).

More detail is provided in [Section 5.6.5](#) on the reasons for responses that will be included in the analysis datasets.

3.2.2 Main analytical approach

The primary endpoint of the ORR will be summarized with the corresponding 2-sided exact 95% confidence intervals (CI) based on the Clopper-Pearson method in each cohort by dose level of SAR444881 in the treated population.

The BOR will also be summarized in the treated population in each cohort by dose level of SAR444881.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are secondary efficacy endpoints: PFS, DCR and DoR. PFS, DCR and DoR will be derived based on the overall (or time point) response assessments from the site. Other secondary endpoints analyses are defined in [Section 3.6.2](#) (TEAE, SAE), [Section 3.7.1.1](#) (PK) and [Section 3.7.1.2](#) (immunogenicity).

3.3.1 Key/Confirmatory secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

3.3.1.1.1 Progression-free survival

Progression-free survival 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.

Progression-free survival will be derived in months, as:

$$(\text{Date of outcome (event or censoring)} - \text{date of first dose of IMP} + 1)/30.4375.$$

Participants without documented progression or death before the analysis COD will be censored at the date of the last evaluable tumor assessment not showing documented progression before the start of further anti-cancer therapy. A participant without a PFS event (death or documented

progression) and without any evaluable post-baseline tumor assessments will be censored at the date of first IMP intake (Day 1).

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 PD.

Event and censoring scheme are summarized in [Table 5](#).

Table 5 - Event and censoring definitions for PFS

Situation	Date of outcome	Outcome	Category
No baseline tumor assessment ^a	Date of first intake of any IMP	Censored	No baseline tumor assessment
No evaluable post-baseline tumor assessment ^a	Date of first intake of any IMP	Censored	No evaluable post-baseline tumor assessment
Alive and no documented progression	Date of the last evaluable tumor assessment documenting no progression	Censored	Alive without documented progression
Withdrawn from study with no documented progression	Date of the last evaluable tumor assessment before withdrawal (if any), dose of first intake of any IMP otherwise	Censored	Withdrawn without documented progression
Documented progression (or Death) at or between scheduled visits	Date of progression (or Date of death)	Event	Documented progression (or Death without documented progression)
Documented progression (or Death) occurring after exactly one non-evaluable tumor assessment	Date of progression (or Date of death)	Event	Documented progression (or Death without documented progression)
Documented progression (or Death) occurring after two or more non-evaluable tumor assessments ^b	Date of the last evaluable tumor assessment documenting no progression	Censored	Event occurred after two or more non-evaluable tumor assessments
Clinical/non-radiological progression	Ignored	Ignored	
Initiation of further anti-cancer therapy	Date of the last evaluable tumor assessment before start date of further anti-cancer therapy (if any), dose of first intake of any IMP otherwise	Censored	Initiation of further anti-cancer therapy

^a Except if the participant dies within 17 weeks after the date of first IMP intake in which case a death event outcome will be considered for the PFS with date of outcome corresponding to the date of death.

^b An event occurring at least t weeks (excluded) after the last evaluable tumor assessment. The value of t is 17 in the first 25 weeks from the first dose of study medication, 22 when the time from first dose of study medication is >25 and ≤38 weeks and 26 when the time from first dose of study medication is > 38.

It is acknowledged that an assessment may include several methods of evaluation performed over a period of several days within a window of time around an expected assessment date. For each tumor assessment, a single date will be derived according to the overall response of that assessment. The date of target lesion(s) assessment will be derived based on the date of the last assessment of target lesion(s).

When the overall response is different from PD, the date of tumor assessment is defined as the date of the last evaluation included in the series of evaluations performed within that time point (i.e., target lesion(s), non-target lesions(s) and new lesion(s) assessments). When the overall response is PD, the date of tumor assessment is the date when progression was first demonstrated according to the target lesion(s), non-target lesion(s) and new lesion(s), as specified below:

- For progression based on new lesion(s) the date of progression is the earliest date a new lesion has been detected.
- For progression based on non-target lesion(s), the date of progression is the date of the last assessment of non-target lesion(s).
- For progression based on target lesion(s), the date of progression is the date of the last assessment of target lesion(s).

If progression is based on several events within the same tumor assessment (e.g., new lesion(s) seen along with target lesion(s) progression), the earliest date of progression, according to the rules listed above, will be the date of assessment.

3.3.1.1.2 Disease control rate

The DCR is defined as the proportion of the participants in the population of interest whose BOR is either confirmed CR or PR, or SD that is at least 49 days after first dose of IMP (i.e. a minimum of 8 weeks minus the 7-days visit window). Participants in the specified population of interest who do not meet the criteria for a BOR of CR, PR or SD will be included in the denominator as participants without disease control.

3.3.1.1.3 Duration of response

Duration of response (DoR) for a participant with a BOR of confirmed CR or PR is defined as the time between the date of first confirmed response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.

Duration of response will be derived in months, as:

$$[\text{Date of outcome (event or censoring)} - \text{date of first confirmed CR/PR} + 1] / 30.4375.$$

The outcome rules are the same as described for PFS ([Table 5](#)) in [Section 3.3.1.1.1](#).

The date of the first confirmed response corresponds to the date to the first overall response of CR or PR that is confirmed by an overall response of CR or PR at least 4 weeks later. For example,

- If a participant has PR followed by CR ≥ 4 weeks (28 days) later, then the BOR will be PR and the date of PR will be used as the date of the first confirmed response.

If a participant has PR followed by CR ≥ 4 weeks (28 days) later, which is in turn followed by another CR ≥ 4 weeks (28 days) later, then the BOR will be CR but the date of PR will be used as the date of first confirmed response..

3.3.1.2 Main analytical approach

3.3.1.2.1 Progression-free survival

Progression-free survival will be summarized in each cohort by dose level of SAR444881 in the treated population.

The PFS rate (PFSR) estimate by the Kaplan-Meier (K-M) method and corresponding 95% CI will be derived based on the Greenwood formula and presented at 3, 6, 9, 12 and up to 24 months. Median PFS using the K-M method and corresponding 2-sided 95% CI derived using the Brookmeyer-Crowley method will be summarized and K-M plots presented.

3.3.1.2.2 Disease control rate

The DCR will be summarized with the corresponding 2-sided exact 95% CI based on the Clopper-Pearson method in each cohort by dose level of SAR444881 in the treated population.

3.3.1.2.3 Duration of response

The survival rate estimate for the DoR by the K-M method and corresponding 95% CI will be derived based on the Greenwood formula and presented at 3, 6, 9, 12 and up to 24 months. Median DoR using the K-M method and corresponding 2-sided 95% CI derived using the Brookmeyer-Crowley method will be summarized and K-M plots presented for DoR in each cohort by dose level of SAR444881 in the treated population.

3.3.2 Supportive secondary endpoint(s)

The time to first response, time to best response and best percentage change from baseline in the sum of the diameters of target lesions will be presented as supportive secondary endpoints.

3.3.2.1 Definition of endpoint(s)

3.3.2.1.1 Time to first response

The time to first response for a participant with a BOR of confirmed CR or PR per RECIST v1.1 is defined as the time between the first dose of IMP and the date of first confirmed response of CR or PR as defined in [Section 3.3.1.1.3](#).

Time to first response will be derived in months, as:

$$[\text{Date of first confirmed CR/PR} - \text{date of first dose of IMP} + 1]/30.4375.$$

3.3.2.1.2 Time to best response

The time to best response is the time to the date of the first occurrence of the BOR for participants with a BOR of confirmed CR or PR per RECIST v1.1 as defined in [Section 3.2.1.1](#). For example,

if a patient has an overall response of PR > SD > PR > CR > CR all at least 4 weeks apart, then the time to best response will be the time from first dose of IMP to the date of the first instance of CR.

Time to best response will be derived in months, as:

$$[\text{Date of BOR} - \text{date of first dose of IMP} + 1] / 30.4375$$

3.3.2.1.3 Best percentage change from baseline in the sum of the diameters of target lesions

The percentage change from baseline in the sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) is derived for all post-baseline assessments up to and including the date of first objectively documented disease progression, death, the date of first dose of subsequent anti-cancer therapy or the COD (whichever occurs first) and is defined as:

$$\frac{(\text{Sum of diameters at the post-baseline assessment} - \text{sum of diameters at baseline})}{\text{Sum of diameters at baseline}} \times 100.$$

The best percentage change from baseline in the sum of the diameters is defined as the minimum percentage change from baseline in the sum of the diameters observed across the post-baseline assessments. This represents the maximum decrease or the minimum increase, if there is no decrease, in target lesion size observed. The best percentage change from baseline will be missing for participants who have no target lesions at baseline, who are missing the sum of diameters for target lesions at baseline or have no available sum of diameters for target lesions post-baseline.

3.3.2.2 Main analytical approach

3.3.2.2.1 Time to first response

The median time to first response will be summarized in each cohort by dose level of SAR444881 in the treated population.

3.3.2.2.2 Time to best response

The median time to best response will be summarized in each cohort by dose level of SAR444881 in the treated population.

3.3.2.2.3 Best percentage change from baseline in the sum of the diameters of target lesions

The best percentage change will be summarized descriptively in each cohort by dose level of SAR444881 in the treated population.

A waterfall plot will also be provided.. The bars will be presented in decreasing order and color coded by the BOR of the participant.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

3.5 MULTIPLICITY ISSUES

No adjustment will be made for multiplicity.

3.6 SAFETY ANALYSES

All safety analyses will be performed in each cohort separately and by dose level of SAR444881 on the treated population as defined in [Section 2](#), unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the treated population (e.g., exposed but not enrolled/randomized) will be provided.

3.6.1 Extent of exposure

Extent of exposure overall and for each study medication will be summarized in the treated population separately for each cohort by dose level.

The study medications and pre-medications administered in each cohort are detailed below in the order of administration:

- **Cohort A1:** Pembrolizumab, pemetrexed premedication, pemetrexed, carboplatin (for the first 4 cycles only), and SAR444881 administered every 3 weeks (Q3W) in 21-day cycles for up to 35 cycles.
- **Cohort B1:** Pembrolizumab, and SAR444881 administered Q3W in 21-day cycles for up to 35 cycles.
- **Cohort C1 and Cohort E1:** Cetuximab premedication, cetuximab, and SAR444881 administered every 2 weeks (Q2W) in 28-day cycles for up to 2 years.
- **Cohort D1:** Monotherapy SAR444881 administered Q2W in 28-day cycles for up to 2 years.

IMP/study medication refers to SAR444881, pembrolizumab, cetuximab, pemetrexed and carboplatin. The number of theoretical days until the next administration is 14 days with 28-day cycles in Cohorts C1, D1 and E1 and 21 days with 21-day cycles in Cohorts A1 and B1.

A cycle will be classed as started if at least one infusion is started in the cycle, even if the infusion is only partially administered.

3.6.1.1 Overall exposure

The dose information, considering all study medications, will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any of the study interventions is administered.
- Duration of IMP exposure (in weeks) is defined as (Last day of exposure – first day of exposure +1)/7.
- The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP.

The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:

- The last administration date + the number of theoretical days until the next administration for SAR444881.
- The last administration date + the number of theoretical days until the next administration for pembrolizumab.
- The last administration date + the number of theoretical days until the next administration for cetuximab.
- The last administration date + the number of theoretical days until the next administration for carboplatin.
- The last administration date + the number of theoretical days until the next administration for pemetrexed.

The total number of cycles started, number of cycles started by participants will be summarized as a quantitative variable and by category (number (%) of participants where the number of cycles received is in the category specified). Categories will be defined in approximately 3 monthly intervals of cycles. For cohorts with 28-day cycles, this would be as follows: 1-3 cycles, 4-6 cycles, 7-9 cycles, 10-12 cycles, 13-15 cycles, 16-18 cycles, 19-21 cycles, 22-24 cycles, 25-26 cycles. For cohorts with 21-day cycles, this would be as follows: 1-4 cycles, 5-8 cycles, 9-16 cycles, 17-20 cycles, 21-24 cycles, 25-28 cycles, 29-32 cycles, 33-35 cycles. The duration of overall exposure will be summarized quantitatively.

The following variable will be computed to describe overall dose modification (cycle delay):

- Cycle delay: A cycle is deemed to be delayed if the start date of the current cycle – theoretical duration of a cycle – start date of the previous cycle is > 2 days. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the participant level (with number of participants used as denominator) and cycle level (with number of cycles started used as denominator), as follows:

- Number (%) of participants with a least 1 cycle delayed:

- Number (%) of participants with a cycle delayed between 2 and 7 days (using maximum delay across all cycles).
- Number (%) of participants with a cycle delayed >7 days (using maximum delay across all cycles).
- Number (%) of cycles delayed:
 - Number (%) of cycles delayed between 2 and 7 days.
 - Number (%) of cycles delayed >7 days.

3.6.1.2 SAR444881, Pembrolizumab, Cetuximab, Pemetrexed and Carboplatin exposure

Exposure for SAR444881, pembrolizumab, cetuximab, pemetrexed and carboplatin will be presented separately in addition to the overall exposure described in [Section 3.6.1.1](#). The study medication and the corresponding duration of cycles and the dosing frequency is presented in [Table 6](#) alongside the cohorts where each medication is administered.

Table 6 - Frequency of dosing and cycle duration for study medication

Drug	Cohorts	Treatment frequency	Cycle duration ^a
SAR444881	C1, D1 and E1	Q2W	14-days
SAR444881	A1 and B1	Q3W	21-days
Pembrolizumab	A1 and B1	Q3W	21-days
Cetuximab	C1 and E1	Q2W	14-days
Pemetrexed	A1	Q3W	21-days
Carboplatin	A1	Q3W ^b	21-days

^a Correspond also to the number of theoretical days until the next administration.

^b For 4-cycles only.

For each of the study medications, the dose information will be assessed by the following:

- Total number of infusions started.
- Total number of cycles started.
- Number of infusions started per participant.
- Number of cycles started per participant.
- Duration of exposure (in weeks) is defined by date of last administration + number of theoretical days until the next administration – date of first administration /7.
- Actual dose (mg/kg for SAR444881, mg for pembrolizumab and carboplatin, and mg/m² for cetuximab and pemetrexed).
- Cumulative dose (mg/kg for SAR444881, mg for pembrolizumab and carboplatin, and mg/m² for cetuximab and pemetrexed): the cumulative dose is the sum of all actual doses given from first to last administration.

- Actual dose intensity (ADI in units/week): defined as the cumulative dose divided by the duration of the exposure (in weeks).
- Planned dose intensity (PDI in units/week): corresponds to the planned dose multiplied by the theoretical total number of doses in each cycle and divided by the theoretical cycle duration expressed in weeks (i.e., 4 weeks per cycle started in Cohorts C1 and D1 and 3 weeks per cycle started in Cohorts A1, B1 and E1).
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (units/week)}}{\text{PDI (units/week)}}$.

The total number of infusions started, total number of cycles started, and number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants where the number of cycles received is in the category specified). Categories will be defined in approximately 3 monthly intervals of cycles. For 28-day cycles, this would be as follows: 1-3 cycles, 4-6 cycles, 7-9 cycles, 10-12 cycles, 13-15 cycles, 16-18 cycles, 19-21 cycles, 22-24 cycles, 25-26 cycles. For 21-day cycles, this would be as follows: 1-4 cycles, 5-8 cycles, 9-16 cycles, 17-20 cycles, 21-24 cycles, 25-28 cycles, 29-32 cycles, 33-35 cycles.

In addition, number of infusions started by participant will be summarized as a quantitative variable and by category (number [%] of participants where the number of infusions received is in the category specified). Categories will be defined in approximately 3 monthly intervals of infusions. For 28-day cycles, this would be as follows: 1-6 infusions, 7-12 infusions, 13-18 infusions, 19-24 infusions, 25-30 infusions, 31-36 infusions, 37-42 infusions, 43-48 infusions, 49-52 infusions. For 21-day cycles, this would be as follows: 1-4 infusions, 5-8 infusions, 9-12 infusions, 13-16 infusions, 17-20 infusions, 21-24 infusions, 25-28 infusions, 29-32 infusions, 33-35 infusions.

Duration of exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction for cetuximab, pemetrexed and carboplatin: The first administration will not be counted as a dose reduction. For the second and subsequent administrations, dose reduction will be determined using the dose level intervals provided in the relevant tables below, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 7 - Cetuximab dose reduction criteria

Actual dose level	Dose level interval
Starting dose (■ mg/m ²)	■ mg/m ²
Dose level -1 (■ mg/m ²)	■ mg/m ² and ■ mg/m ²
Dose level -2 (■ mg/m ²)	■ mg/m ²

Table 8 - Pemetrexed dose reduction criteria

Actual dose level	Dose level interval
Starting dose (■ mg/m ²)	■ mg/m ²
Dose level -1 (■ mg/m ²)	■ mg/m ² and ■ mg/m ²
Dose level -2 (■ mg/m ²)	■ mg/m ²

Table 9 - Carboplatin dose reduction criteria

Actual dose level	Dose level interval
Starting dose (AUC 5, maximum dose ■ mg)	■ mg
Dose level -1 (AUC 3.75, maximum dose ■ mg)	■ mg and ■ mg
Dose level -2 (AUC 2.5, maximum dose ■ mg)	■ mg

- Dose omission defined as a dose not administered at the scheduled visit.
- Dose delay for SAR444881 defined as a dose where the start date of the dose – theoretical duration of time between doses – start date of the previous dose is > 2 days (does not apply to the first dose) or if SAR444881 is administered on a date that is after the date of administration of any of the combination agents administered for the same dosing visit in Cohorts A1, B1, C1 and E1.
- Dose delay for pembrolizumab and cetuximab is defined as a dose where the start date of the dose – theoretical duration of time between doses – start date of the previous dose is > 2 days (does not apply to the first dose).
- Dose delay for pemetrexed is defined as a dose where the start date of the dose – theoretical duration of time between doses – start date of the previous dose is > 2 days (does not apply to the first dose) or if pemetrexed is administered on a date that is after the date of administration of pembrolizumab for the same cycle.
- Dose delay for carboplatin is defined as a dose where the start date of the dose – theoretical duration of time between doses – start date of the previous dose is > 2 days (does not apply to the first dose) or if carboplatin is administered on a date that is after the date of administration of pembrolizumab and pemetrexed for the same cycle.
- Dose interruption is defined as a dose where the administration is stopped during an infusion and will be classified into two categories: 1) dose interrupted and restarted, 2) dose interrupted and not restarted.

Note: Dose reductions are not allowed for SAR444881 and pembrolizumab in Part 2 of the study.

Dose modifications and dose interruptions will be analyzed by participant, cycle and infusion as follows:

- **Participant** (number of participants treated will be used as denominator)
 - Number (%) of participants with at least 1 dose modification.
 - Number (%) of participants with at least 1 dose delayed.

- Number (%) of participants with at least 1 dose reduction (for cetuximab, pemetrexed and carboplatin only).
- Number (%) of participants with at least 1 dose omission.
- Number (%) of participants with at least 1 dose interruption.
 - Number (%) of participants with at least 1 dose interruption restarted.
 - Number (%) of participants with at least 1 dose interruption definitively stopped.
- **Cycle** (number of cycles started will be used as denominator)
 - Number (%) of cycles with at least 1 dose modification.
 - Number (%) of cycles with at least 1 dose delayed.
 - Number (%) of cycles with at least 1 dose reduction (for cetuximab, pemetrexed and carboplatin only).
 - Number (%) of cycles with at least 1 dose omission.
 - Number (%) of cycles with at least 1 dose interruption.
 - Number (%) of cycles with at least 1 dose interruption restarted.
 - Number (%) of cycles with at least 1 dose interruption definitively stopped.
- **Infusion** (number of infusions started will be used as denominator)
 - Number (%) of infusions with at least 1 dose modification.
 - Number (%) of infusions with at least 1 dose delayed.
 - Number (%) of infusions with at least 1 dose reduction (for cetuximab, pemetrexed and carboplatin only).
 - Number (%) of infusions with at least 1 dose omission.
 - Number (%) of infusions with at least 1 dose interruption.
 - Number (%) of infusions with at least 1 dose interruption restarted.
 - Number (%) of infusions with at least 1 dose interruption definitively stopped.

3.6.2 Adverse events

General common rules for adverse events

All AEs will be graded according to the National Cancer Institute Common Terminology for AEs (NCI-CTCAE version 5.0) and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened, or became serious during the TE period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, TE and post-treatment periods.

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

An AE with an incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

AEs are classed as related to a study medication if the relationship is possibly related or related. If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as possibly related to IMP. Missing grade or severity will be left as missing.

Multiple occurrences of the same event for the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for grade ≥ 3 (including grade 5). Missing grades, if any, will be included in the “all grades” category.

The AE tables will be sorted as indicated in [Table 10](#).

Table 10 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order (defined in the introductory guide for the MedDRA version used) and decreasing frequency of PTs ^{a,b}
PT	By decreasing frequency of PTs ^a

^a Sorting will be based on the incidence in highest dose level of SAR444881.

^b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (e.g., treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE.
- Any grade ≥ 3 TEAE.
- Any TE SAE.
- Grade 5 TEAE (any TEAE with a fatal outcome during the TE period).
- Any TEAE leading to permanent intervention discontinuation (for Cohort D1 only).

- Any TEAE leading to permanent full intervention discontinuation (for Cohorts A1, B1, C1 and E1 only).

If the study medications are not all discontinued at the same time, then the action taken for the last study medication stopped will be used.

- Any TEAE leading to permanent intervention discontinuation for each study medication.
 - Any TEAE leading to permanent discontinuation of SAR444881 (for Cohorts A1, B1, C1 and E1 only).
 - Any TEAE leading to permanent discontinuation of pembrolizumab (for Cohorts A1 and B1 only).
 - Any TEAE leading to permanent discontinuation of cetuximab (for Cohorts C1 and E1 only).
 - Any TEAE leading to permanent discontinuation of pemetrexed (for Cohort A1 only).
 - Any TEAE leading to permanent discontinuation of carboplatin (for Cohort A1 only).
- Any TEAE related to study medication.
 - Any TEAE related to SAR444881.
 - Any TEAE related to pembrolizumab (for Cohorts A1 and B1 only).
 - Any TEAE related to cetuximab (for Cohorts C1 and E1 only).
 - Any TEAE related to pemetrexed (for Cohort A1 only).
 - Any TEAE related to carboplatin (for Cohort A1 only).
- Any TE SAE related to study medication.
 - Any TE SAE related to SAR444881.
 - Any TE SAE related to pembrolizumab (for Cohorts A1 and B1 only).
 - Any TE SAE related to cetuximab (for Cohorts C1 and E1 only).
 - Any TE SAE related to pemetrexed (for Cohort A1 only).
 - Any TE SAE related to carboplatin (for Cohort A1 only).
- Any grade ≥ 3 TEAE related to study medication.
 - Any grade ≥ 3 TEAE related to SAR444881.
 - Any grade ≥ 3 TEAE related to pembrolizumab (for Cohorts A1 and B1 only).
 - Any grade ≥ 3 TEAE related to cetuximab (for Cohorts C1 and E1 only).
 - Any grade ≥ 3 TEAE related to pemetrexed (for Cohort A1 only).
 - Any grade ≥ 3 TEAE related to carboplatin (for Cohort A1 only).

Permanent intervention discontinuation for each study medication included all AEs leading to permanent discontinuation of the specified intervention, regardless of whether or not other study medications continue without the specified intervention after the permanent discontinuation.

The AE summaries of [Table 11](#) will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥ 3 .

Table 11 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
Common TEAE ($\geq 10\%$ in at least 1 dose level within the specified Cohort)	Primary SOC and PT
TEAE related to any study medication as per Investigator's judgment	Primary SOC and PT
TEAE related to SAR444881 as per Investigator's judgment	Primary SOC and PT
TEAE related to pembrolizumab as per Investigator's judgment (for Cohorts A1 and B1 only)	Primary SOC and PT
TEAE related to cetuximab as per Investigator's judgment (for Cohorts C1 and E1 only)	Primary SOC and PT
TEAE related to pemetrexed as per Investigator's judgment (for Cohort A1 only)	Primary SOC and PT
TEAE related to carboplatin as per Investigator's judgment (for Cohort A1 only)	Primary SOC and PT
TE SAE	Primary SOC and PT
TE SAE related to any study medication as per Investigator's judgment	Primary SOC and PT
TE SAE related to SAR444881 as per Investigator's judgment	Primary SOC and PT
TE SAE related to pembrolizumab as per Investigator's judgment (for Cohorts A1 and B1 only)	Primary SOC and PT
TE SAE related to cetuximab as per Investigator's judgment (for Cohorts C1 and E1 only)	Primary SOC and PT
TE SAE related to pemetrexed as per Investigator's judgment (for Cohort A1 only)	Primary SOC and PT
TE SAE related to carboplatin as per Investigator's judgment (for Cohort A1 only)	Primary SOC and PT
TEAE leading to permanent intervention discontinuation (for Cohort D1 only)	Primary SOC and PT
TEAE leading to permanent full intervention discontinuation (for Cohorts A1, B1, C1 and E1 only)	Primary SOC and PT
TEAE leading to permanent intervention discontinuation of SAR444881 (for Cohorts A1, B1 C1 and E1 only)	Primary SOC and PT
TEAE leading to permanent intervention discontinuation of pembrolizumab (for Cohorts A1 and B1 only)	Primary SOC and PT
TEAE leading to permanent intervention discontinuation of cetuximab (for Cohorts C1 and E1 only)	Primary SOC and PT
TEAE leading to permanent intervention discontinuation of pemetrexed (for Cohort A1 only)	Primary SOC and PT
TEAE leading to permanent intervention discontinuation of carboplatin (for Cohort A1 only)	Primary SOC and PT
TEAE leading to death ^b	Primary SOC and PT
TEAE leading to death ^b related to any study medication as per Investigator's judgment	Primary SOC and PT
TEAE leading to death ^b related to SAR444881 as per Investigator's judgment	Primary SOC and PT
TEAE leading to death ^b related to pembrolizumab as per Investigator's judgment (for Cohorts A1 and B1 only)	Primary SOC and PT
TEAE leading to death ^b related to cetuximab as per Investigator's judgment (for Cohort C1 only)	Primary SOC and PT
TEAE leading to death ^b related to pemetrexed as per Investigator's judgment (for Cohort A1 only)	Primary SOC and PT
TEAE leading to death ^b related to carboplatin as per Investigator's judgment (for Cohort A1 only)	Primary SOC and PT

Type of AE	MedDRA levels
AE leading to death ^b	Primary SOC and PT
- In context of disease progression ^c	
- In context other than disease progression ^d	
Pre-treatment AE	Primary SOC and PT
Post-treatment AE	Overview ^a
Post-treatment SAE	Primary SOC and PT
TEAE leading to dose modification of SAR444881 (including dose delay and dose omission)	Primary SOC and PT
TEAE leading to dose modification of pembrolizumab (including dose delay and dose omission) (for Cohorts A1 and B1 only)	Primary SOC and PT
TEAE leading to dose modification of cetuximab (including dose delay, dose reduction and dose omission) (for Cohort C1 and E1 only)	Primary SOC and PT
TEAE leading to dose modification of pemetrexed (including dose delay, dose reduction and dose omission) (for Cohort A1 only)	Primary SOC and PT
TEAE leading to dose modification of carboplatin (including dose delay, dose reduction and dose omission) (for Cohort A1 only)	Primary SOC and PT
TEAE leading to dose interruption of SAR444881 (including dose delay and dose omission)	Primary SOC and PT
TEAE leading to dose interruption of pembrolizumab (including dose delay and dose omission) (for Cohorts A1 and B1 only)	Primary SOC and PT
TEAE leading to dose interruption of cetuximab (including dose delay, dose reduction and dose omission) (for Cohorts C1 and E1 only)	Primary SOC and PT
TEAE leading to dose interruption of pemetrexed (including dose delay, dose reduction and dose omission) (for Cohort A1 only)	Primary SOC and PT
TEAE leading to dose interruption of carboplatin (including dose delay, dose reduction and dose omission) (for Cohort A1 only)	Primary SOC and PT

^a Will include the following AE categories: any AEs, any SAEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation (in Cohort D1), any AEs leading to permanent full intervention discontinuation (in Cohort A1 B1, C1 and E1).

^b Death as an outcome of the AE as reported by the Investigator in the AE page.

^c Death within 90 days from last IMP administration and the cause of death is disease progression.

^d Death within 90 days from last IMP administration and for whom cause of death is not disease progression or the death occurred more than 90 days from last IMP administration and the cause of death is AE.

Analysis of deaths

In addition to the analyses of deaths included in [Table 11](#), the number (%) of participants in the following categories will be provided:

- Deaths during the TE and post-treatment periods by main reason for death.
- An overview of Grade 5 AEs will be provided with the following categories:
 - Grade 5 AE (TEAE and post-treatment).
 - Fatal TEAE (regardless of date of death/period).
 - Grade 5 TEAE with a fatal outcome during the treatment-emergent period.
 - Any Grade TEAE with a fatal outcome during the post-treatment period.

- Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) are not defined for this study. Other AEs of interest will be selected for analyses as indicated in Table 12. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 10.

Table 12 - Selections for other AEs of interest

Other AEs of interest	Selection
Immune-mediated AEs (imAEs)	eCRF specific tick box on the AE page
Events of clinical interest (ECI)	eCRF specific tick box on the AE page for overdose and elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
DLT	eCRF specific tick box on the AE page

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and ECG variables are collected. They will be converted into standard international units.

- Hematology:
 - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, platelet count, prothrombin time [expressed as international normalized ratio (INR)], activated partial thromboplastin time (PTT).
 - White blood cells: white blood cell count including differentials (absolute and % neutrophils, lymphocytes, monocytes, basophils and eosinophils).
- Clinical chemistry:
 - Metabolism: glucose, total protein, albumin, creatinine kinase/creatinine phosphokinase, lipase, amylase, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) (for Cohorts C1 and D1, T3 and T4 are only if TSH is abnormal).
 - Electrolytes: sodium, potassium, calcium corrected, phosphorus, magnesium.

$$\text{Calcium corrected (mmol/L)} = \text{total calcium (mmol/L)} + 0.8 * 0.25 * [4 - \text{serum albumin (g/L)} * 0.1].$$
 - Renal function: creatinine, creatinine clearance (screening only), blood urea nitrogen (BUN), uric acid.
 Creatinine clearance will be derived with the equation of Cockcroft and Gault using weight assessed at the same visit as creatinine.

- Liver function: ALT, AST, alkaline phosphatase, gamma glutamyl transferase (GGT) (only if liver function test is abnormal), lactate dehydrogenase (LDH), total and direct bilirubin (only if total bilirubin is abnormal).
- Pregnancy test: serum β -human chorionic gonadotropin (all female participants).
- Serology (screening only): hepatitis B surface antigen (HBsAg), anti-hepatitis-C virus (HCV) antibody or HCV ribonucleic acid (RNA), human immunodeficiency virus (HIV)-1, HIV-2.
- Other: follicle stimulating hormone (FSH) (screening only).
- Urinalysis:
 - Urinalysis for quantitative analysis: pH, specific gravity, proteins, glucose, blood, leukocyte esterase.
- Vital signs: heart rate, pulse rate, systolic and diastolic blood pressure (sitting), respiratory rate, temperature, weight, body mass index, body surface area, height (at screening only), Eastern Cooperative Oncology Group (ECOG) performance status.
- ECG variables: heart rate, PR interval, QRS duration, QT interval, and corrected QT interval according to Fridericia (QTcF). ECG assessments will also be described as normal, abnormal – not clinically significant or abnormal – clinically significant.

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification (ULOQ) will be replaced by ULOQ value.

For laboratory tests not covered by Common Terminology Criteria for Adverse Events (CTCAE), results will be graded by low [below the lower limit of normal (LLN)], normal and high [above the upper limit of normal (ULN)] classifications where possible. For hematological and biochemistry parameters, grading will be derived using local laboratory normal ranges.

Quantitative analyses

When relevant, for vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each planned visit, and the worst value (minimum and/or maximum value depending on the parameter) during the TE period. These analyses will be performed using local measurements for laboratory variables and ECG variables.

When relevant, for vital signs and ECG variables above, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to PCSA and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version 5.0). In addition, for laboratory variables for which NCI-CTCAE scale is not applicable, vital signs and ECG variables, potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA and NCI grading will be performed based on the worst value during the TE period, using all measurements (either scheduled, unscheduled or repeated).

For laboratory variables graded by NCI-CTCAE:

- The number (%) of participants by worst grade during the TE period according to the baseline grade will be presented. This is equivalent to a shift table using CTCAE grade to compare baseline to the worst on-treatment value.

For laboratory variables not graded by NCI-CTCAE:

- The number (%) of participants with a PCSA or out-of-range values during the TE period according to the baseline status will be presented. This is equivalent to a shift table using low/normal/high classification to compare baseline to the worst on-treatment value.

For vital signs and ECG data, the worst interpretation during the TE period will be summarized regardless of the baseline level and according to the baseline interpretation (the latter is equivalent to a shift table comparing baseline to worst on-treatment result). The worst interpretation is assigned in the following order from worst to best: abnormal, clinically significant; abnormal, not clinically significant; and normal. The following baseline status categories will be used:

- Normal/missing.
- Abnormal, not clinically significant.
- Abnormal, clinically significant.

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- A graph of the distribution of peak values of ALT or AST versus peak values of total bilirubin during the treatment-emergent period.
- The number of participants with abnormalities at baseline.
- The number of participants with abnormalities (PCSA e.g., ALT >5 ULN) during the TE period.
- The number of participants with abnormalities (NCI-CTCAE) during the TE period.

3.6.3.2 Physical examination

Abnormal physical examination findings will be presented in a by-participant data listing.

3.6.3.3 Left ventricular ejection fraction and troponin

Left ventricular ejection fraction (LVEF) and troponin will be collected at screening and as clinically indicated. These data will be presented in by-participant data listings.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

The PK of SAR444881 will be assessed 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 exposure-response (ER) analysis, which will be presented in a separate report. In addition, model-determined exposures may be used for ER analyses.

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

Table 13 - List of PK parameters and definition

Parameters	Definition
C _{max}	Maximum observed serum concentration
C _{eo}	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 to maximum observed serum concentration
AUC _(0-τ)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC _(inf)	Area under the serum concentration-time curve from time zero extrapolated to infinite time

Serum samples for pembrolizumab and cetuximab are collected during the dose optimization/expansion component of the study. These samples are stored for potential analysis if further investigations are needed.

The derivation of the PK parameters for SAR888441, the population PK modelling and any details relating to PK parameters of pembrolizumab and cetuximab (if required) will be detailed in a separate PK analysis plan.

PK data will be summarized in the PK population separately for each cohort by dose level of SAR888441 using all nominal sampling time points.

The PK serum concentrations for SAR888441 will be summarized using the following descriptive statistics: arithmetic mean, standard deviation, standard error of the arithmetic mean, median, minimum, maximum, geometric mean, and coefficient of variation (%). In addition, means ± the standard deviation of the serum concentrations for SAR888441 will be plotted by visit with a line per dose level. Individual serum concentrations of SAR444881 will be listed in a by-participant listing at each nominal sampling time point.

3.7.1.2 Immunogenicity analyses

Participant ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the immunogenicity population separately for each cohort by dose level of SAR444881 for each ADA assayed (e.g., neutralizing ADA), separately.

Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately. Time to ADA onset (or boost) and duration of ADA (or boosted response) will be described with minimum, Q1, median, Q3 and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Participant's ADA status

- Participants with **pre-existing ADAs** correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing or non-reportable ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
 - Participants with **treatment-induced ADAs** correspond to participants with ADAs that developed during the TE period and without pre-existing ADA (including participants without pre-treatment samples).
 - Participants with **treatment-boosted ADAs** correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. At least a 4-fold increase in titers for 2-fold serial dilution schema (or 9-fold increase in titers for 3-fold serial dilution schema) will be considered as significant.
- Participants with **unclassified ADA** correspond to participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (i.e., a positive ADA sample during the TE period in a participant with pre-existing ADA but with missing titer at this sample or at baseline).
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample nor unclassified ADA during the TE period.
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without TE ADA (i.e. ADAs are not detected in a sample, but a negative result cannot be incontrovertibly confirmed).
- Participants with cross-reactivity with endogenous protein(s) and/or cross-neutralization of endogenous protein(s).

Kinetics of ADA response

Kinetics of ADA response will be derived for participants with treatment-induced/boosted ADA considering ADA samples collected during the TE period and post-treatment period.

- **Time to onset of ADA response** is defined as the time period between the first SAR444881 administration and the first treatment-induced/boosted ADA. The ‘median time to ADA development (or boost)’ and the quartiles Q1 and Q3 should be reported.
- **Duration of ADA response** is defined as the time between the first treatment-induced/boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ADA duration will be summarized only for participants with persistent ADA response.
- **Persistent ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
- **Transient ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of less than 16 weeks and the last sample of the TE period is not treatment-induced/boosted.
- **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient (i.e. only the last timepoint is positive or the last 2 samples separated by less than 16 weeks are positive).

ADA response variable:

- **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.7.1.4 Biomarker analyses

3.8 INTERIM ANALYSES

The following analyses will be performed during the study:

- Data from the safety run-in of Cohort A1 will be reviewed by the SRC.
- Continuous evaluation of toxicity will be performed throughout Part 2 of the study.
- An IA will be performed in each cohort at the end of Stage 1.
- An analysis will be performed in each cohort at the end of Stage 2, if Stage 2 is conducted.
- Additional IAs on efficacy may also be conducted at various times prior to study completion to facilitate program decisions and to support scientific publications or presentations.

3.8.1 Safety Review Committee

A 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.

- Overall summary of TEAEs.

TEAEs by SOC and PT.

- TEAEs by relationship to study medication by SOC.
- Vital signs parameters by visit.

Swimmer plot of study duration. The following data presentations are detailed in the current version of the SRC charter but will not be produced for the SRC meetings:

- Plot of incidence of TEAEs related to study drug.
- TEAEs by CTCAE grade, SOC and PT

3.8.3 Continuous evaluation of toxicity

If, at any time, the aggregate rate of TEAEs 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 TE life-threatening SAEs, 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.

Continuous evaluation of toxicity events will be performed throughout enrollment for all optimization/expansion cohorts. Bayesian toxicity monitoring on DLT (Trial Design [Online]. [cited May 18, 2022]. Available from: <https://trialdesign.org/one-page-shell.html#BTOX>) is used to determine the stopping boundaries based on the following assumptions: maximum probability of DLT allowed = 0.3, prior distribution for DLT rate: Beta (1,1), minimum number of participants before early stopping rule applies = 6, cohort size = 1, and posterior probability of DLT rate > 0.3 is at least 80%. Table 14 shows the number of participants with AEs meeting DLT criteria before enrollment in the trial will be paused until an appropriate evaluation of the cause of DLT is conducted by the Study Board and a correction plan is established.

Table 14 - Bayesian toxicity monitoring plan in dose optimization/expansion phase

N	6-8	9-11	12-15	16-18	19-22	23-25	26-29	30-32	33-36	37-39	40
n	≥3	≥4	≥5	≥6	≥7	≥8	≥9	≥10	≥11	≥12	≥13

Abbreviations: N total number of participants evaluated. n: number of participants with AEs meeting DLT criteria.

3.8.4 Interim analysis at the end of Stage 1 of each cohort

An IA 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. IA 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.

The sponsor will also 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 (see [Sections 5.2.1](#) and [5.2.2](#) for more details on the two-stage design and go/no-go decisions).

3.8.5 Primary analysis at the end of Stage 2 of each cohort

The primary analysis in each cohort at the end of Stage 2 will be the date approximately 9 months after the last participant's last dose of study medication in the cohort or early discontinuation of all study medication, whichever comes first. As with the IA at the end of Stage 1, the sponsor will also 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. Details on the interpretation of the ORR at the end of Stage 2 are provided in [Section 5.2.2](#).

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in protocol amendments. There were no major statistical changes in the protocol up to the protocol version dated 13-May-2024 used as the basis for SAP version 2.0.

The changes in [Table 15](#) below were made to SAP version 2.0 as part of the amendment and are changes from the protocol dated 13-May-2024. These changes may be implemented in a future amendment of the protocol to ensure that the SAP and protocol are consistent in these aspects of the statistical analysis.

Table 15 - Major statistical changes from protocol amendment 12

Protocol Amendment Number	Protocol Approval Date	Changes	Rationale
12	13-May-2024	The response-evaluable population is defined in Section 11.2 of the protocol but is not included in the SAP version 2.0.	FDA feedback

Protocol Amendment Number	Protocol Approval Date	Changes	Rationale
		In the protocol Section 11.3.1, the specified analysis population for the interim efficacy analyses is the response-evaluable population and this is the treated population in the SAP version 2.0.	

4 SAMPLE SIZE DETERMINATION

4.1 DOSE OPTIMIZATION/EXPANSION

The purpose of dose optimization/expansion (Part 2) is to assess preliminary anti-tumor activity, and collect additional safety, PK and PD 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 16](#) lists estimated ORR and the corresponding 95% exact CIs by number of responders.

Table 16 – Estimated 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.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

1L:	first line
2L:	second line
2L+:	second line or later
3L:	third line
τ_1 :	target log-odds difference between the objective response rate of the investigational treatment regimen and that of the standard of care
τ_2 :	target log-odds difference between the two dose levels
ADA:	anti-drug antibodies
ADI:	actual dose intensity
AE:	adverse event
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
AUC:	area under concentration-time curve
AUC _(0-τ) :	area under concentration-time curve from time zero to the last quantifiable concentration
AUC _(inf) :	area under concentration-time curve from time zero extrapolated to infinite time
BMI:	body mass index
BOR:	best overall response
BRAF:	v-Raf murine sarcoma viral oncogene homolog B
BSA:	body surface area
BUN:	blood urea nitrogen
C:	study cycle
cetux:	cetuximab
chemo:	chemotherapy (carboplatin/pemetrexed)
CI:	confidence interval
C _{max} :	maximum observed concentration
C _{eoI} :	concentration observed at the end of an intravenous infusion
COD:	cut-off date
CR:	complete response
CRC:	colorectal cancer
CSP:	clinical study protocol
CSR:	clinical study report
CT:	computerized tomography
CTCAE:	Common Terminology Criteria for Adverse Events
ctDNA:	circulating tumor deoxyribonucleic acid
C _{trough} :	concentration at the end of the dosing level
D:	study day
DCR:	disease control rate
DL:	dose level

DLT:	dose limiting toxicity
DNA:	deoxyribonucleic acid
DO:	dose optimization
DoR:	duration of response
eCRF:	electronic case report form
ECG:	electrocardiogram
ECI:	events of clinical interest
ECOG:	Eastern Cooperative Oncology Group
EOT:	end of treatment
ER:	exposure-response
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FSH:	follicle stimulating hormone
GA:	global alternative
GC:	gastric cancer
GEJ:	gastroesophageal junction adenocarcinoma
GGT:	gamma glutamyl transferase
GN:	global null
H:	higher dose
H&N:	head and neck
HBsAg:	hepatitis B surface antigen
HCC:	hepato-cellular carcinoma
HCV:	hepatitis C virus
HIV:	human immunogenicity virus
HLA:	human leukocyte antigen
HLGT:	high-level group term
HLT:	high-level term
IA:	interim analysis
IFN _γ :	interferon gamma
IgG4:	immunoglobulin G4
imAE:	immune-mediated adverse event
IMP:	investigational medicinal product
Ind:	indication
INR:	international normalized ratio
ITT:	intention-to-treat
IV:	intravenous
K-M:	Kaplan-Meier
KRAS:	Kirsten rat sarcoma virus
L:	lower dose
LDH:	lactate dehydrogenase
LLN:	lower limit of normal

LLOQ:	lower limit of quantification
LLT:	lower-level term
LVEF:	left ventricular ejection fraction
MAD:	maximum administered dose
MedDRA:	Medical Dictionary for Regulatory Activities
MMR:	mismatch repair
MRI:	magnetic resonance imaging
MSI:	microsatellite instability
MTD:	maximum tolerated dose
nADA:	neutralizing anti-drug antibodies
NCI-CTCAE:	National Cancer Institute Common Terminology for Criteria Adverse Events
NE:	not evaluable
NG:	no go
NK:	natural killer
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
PBMC:	peripheral blood mononuclear cell
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic; progressive disease
PD1:	programmed death protein 1
PDI:	planned dose intensity
pembro:	pembrolizumab
PET:	positron emission tomography
PFS:	progression-free survival
PFSR:	progression-free survival rate
PK:	pharmacokinetic
PoC:	proof-of-concept
PR:	partial response
PT:	preferred term
PTT:	partial thromboplastin time
Q1:	lower quartile
Q2W:	every 2 weeks
Q3:	upper quartile
Q3W:	every 3 weeks
Q8W:	every 8 weeks
Q12W:	every 12 weeks
QTcF:	corrected QT interval according to Fridericia
R:	randomized
RAS:	rat sarcoma
RCC:	renal cell carcinoma
RDI:	relative dose intensity
RECIST:	Response Evaluation Criteria in Solid Tumours
RNA:	ribonucleic acid
RO:	receptor occupancy

s ₁ :	tuning parameter for activity of dose level 1 in Stage 1
s ₂ :	tuning parameter for activity of dose level 1 in Stage 2
SAE:	serious adverse event
SAP:	statistical analysis plan
SAR:	SAR444881
SCC:	squamous cell carcinoma
SD:	stable disease
SOC:	system organ class
SRC:	safety review committee
t _{1/2} :	half-life
t ₂ :	tuning parameter for activity of dose level 2 in Stage 2
t ₃ :	triiodothyronine
t ₄ :	thyroxine
TBD:	to be determined
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
T _{max} :	time to reach maximum concentration
TNBC:	triple negative breast cancer
TSH:	thyroid stimulating hormone
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
w ₂ :	tuning parameter for dose optimization between the two doses in Stage 2
WHO-DD:	World Health Organization-Drug Dictionary

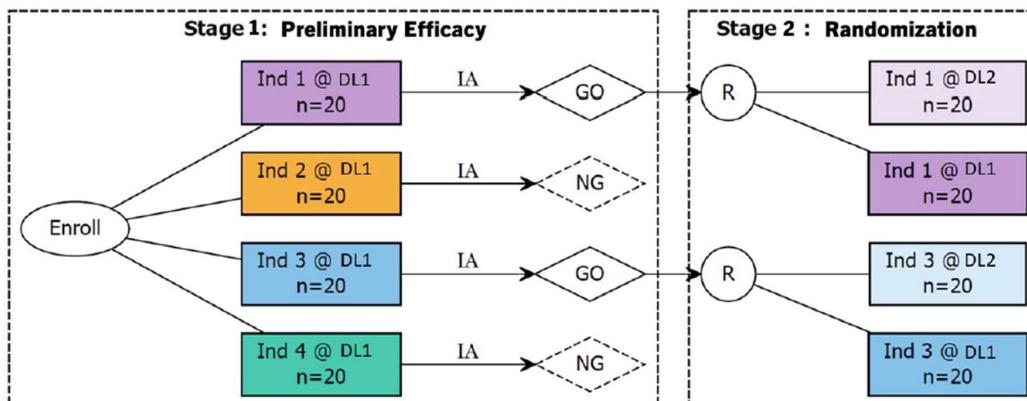
5.2 APPENDIX 2 TWO-STAGE DESIGN

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.

5.2.1 Two-stage design

The design schema is illustrated in [Figure 5](#), 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 IA 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 5 - The two-stage design schema with hypothetical two GO and two No-Go of indications after Stage 1



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 17. 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 0.5 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 15%).

Table 17 - Reference and target ORRs for each indication

Indication	Combination therapy		
Non-squamous NSCLC	SAR444881 + pembrolizumab + carboplatin + pemetrexed as 1L therapy		
NSCLC	SAR444881 + pembrolizumab as 2L and later therapy		
GC/GEJ	SAR444881 + pembrolizumab as 3L and later therapy		
CRC any RAS	SAR444881 + cetuximab as 3L and later therapy		

1L: first line; 2L: second line; 3L: third line; NSCLC: non-small cell lung cancer; GC/GEJ: gastric cancer or gastroesophageal junction adenocarcinoma; CRC: colorectal carcinoma; RAS: rat sarcoma.

At the end of Stage 1, for each indication, an IA will be conducted when 20 patients have undergone at least two post-baseline tumor assessments or have discontinued the study intervention. The posterior probability of $ORR_1 \geq \tau_1$ 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 PoC 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.

5.2.2 Simulation study

Comprehensive simulations are performed to evaluate the performance (operating characteristics) of the two-stage design. The ORR assumptions for DL1 and DL2 across all four indications are tabulated in Table 18. 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 τ_1 to be τ_1 . The minimum difference in ORRs to be distinguished between the two doses is set to be δ .

Results for the interim analysis at the end of Stage 1 are shown in [Table 19](#). For each scenario, the probability of making a Go decision to move from Stage 1 to Stage 2 is calculated by indication.

There are a few key messages:

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.

The number (%) of participants included in each of the analysis populations listed in [Table 3](#) will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled/randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

Regarding intervention discontinuation, the following definitions may be used for Cohorts A1, B1, C1 and E1:

- Permanent **partial** intervention discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued.
- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs. If the study medications are not all discontinued at the same time, then the action taken for the last study medication stopped will be used.

The number (%) of participants in the following categories will be provided:

- Enrolled/randomized participants.
- Enrolled/randomized but not exposed participants.
- Enrolled/randomized and exposed participants.
- Participants still on study intervention (in Cohort D1 only).
- Participants still on any study intervention (in Cohorts A1, B1, C1 and E1 only).
- Participants still on SAR444881 (in Cohorts A1, B1, C1 and E1 only).
- Participants still on pembrolizumab (in Cohorts A1 and B1 only).
- Participants still on cetuximab (in Cohorts C1 and E1 only).
- Participants still on pemetrexed (in Cohort A1 only).
- Participants still on carboplatin (in Cohort A1 only).
- Participants who have permanently discontinued intervention and main reason for permanent intervention discontinuation (in Cohort D1 only).
- Participants who have permanently discontinued SAR444881 and main reason for permanent SAR444881 discontinuation (in Cohorts A1, B1, C1 and E1 only).
- Participants who have permanently discontinued pembrolizumab and main reason for permanent pembrolizumab discontinuation (in Cohorts A1 and B1 only).
- Participants who have permanently discontinued cetuximab and main reason for permanent cetuximab discontinuation (in Cohorts C1 and E1 only).
- Participants who have permanently discontinued pemetrexed and main reason for permanent pemetrexed discontinuation (in Cohort A1 only).
- Participants who have permanently discontinued carboplatin and main reason for permanent carboplatin discontinuation (in Cohort A1 only).
- Participants still on study.
- Participants who are no longer on study and main reason for study discontinuation.

The number (%) of exposed and not enrolled/randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized/enrolled, exposed, with permanent (full) intervention discontinuation and with early study discontinuation will be provided by country and site.

A swimmer plot will be presented in the treated population with bars color coded by dose of SAR444881. The bars will represent the duration of time on study from the date of first dose of IMP with arrows included where the participant is still on study. Symbols will be presented to represent the overall visit response from RECIST assessments positioned on the study day of the scan date. The best overall response and the reason for study discontinuation will be annotated on the plot. Symbols will also be included to represent the study day of the start date of any SAEs, the date of first dose of any subsequent therapy and the date of death.

Protocol deviations

Important and non-important protocol deviations will be summarized in the treated population. Protocol deviations are identified both manually, and in some cases, programmatically. All protocol deviations regardless of how these are identified are reviewed and categorized as important and non-important protocol deviations.

5.4 APPENDIX 4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the treated population.

Demographic and baseline characteristics:

- Age in years as quantitative variable and in categories (<65, 65 to <75, ≥75).
- Sex (Male, Female, Undifferentiated).
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not permitted per local regulation).
- Race subcategory for Asian participants (Asian Indian, Chinese, Japanese, Korean, Thai, Other Asian).
- Ethnicity (Hispanic or Latino, not Hispanic or Latino).
- Weight at baseline in kg.
- Height at baseline in cm.
- Body mass index (BMI) at baseline in kg/m² as collected on the physical measurements eCRF.

- Body surface area (BSA) at baseline in m² will be derived using the Du Bois formula where weight is in kg and height is in cm in the formula below where baseline weight and height are recorded and the baseline BSA is not available:

$$BSA = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}.$$

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

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) and all surgeries. Medical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Specific disease history includes disease status, diagnosis (indication), time since initial diagnosis in months, KRAS mutation tumor status, v-Raf murine sarcoma viral oncogene homolog B (BRAF) mutation tumor status, MSI tumor status, MMR tumor status, tumor mutation burden status and number of mutations.

The time since initial diagnosis in months will be defined as:

$$(\text{Date of first dose of IMP} - \text{date of diagnosis})/30.4375.$$

The time since initial diagnosis will not be derived for partial or missing dates of diagnosis.

Other baseline characteristics include ECOG performance status, reproductive status, and smoking, alcohol and drug abuse history.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first of any IMP intake. Prior medications can be discontinued before first administration or can be ongoing during the on-treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any IMP(s) during the on-treatment period.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post (for example, in the case of missing or partial dates), it will be considered as prior, concomitant, and post-treatment medication.

The prior, concomitant and post-treatment medications will be summarized for the treated population, by anatomic and therapeutic level. In case of equal frequency, alphabetical order will

be used. Participants will be counted once in each anatomical therapeutic chemical (ATC) category (anatomic or therapeutic) linked to the medication.

Anti-cancer therapies

Prior anti-cancer therapies include chemotherapy, hormonotherapy, surgery, radiotherapy, bone marrow transplant, targeted therapies and radiation therapies.

Prior anti-cancer therapies will be listed in the treated population for each cohort separately by dose level of SAR444881. The number of patients who received at least one of the different types of therapies (drug therapies, surgeries and radiotherapy), different types of drug therapies (brachytherapy, gamma knife, stereotactic, radiotherapy, external beam radiation, intensity-modulated therapy), different types of radiotherapies (endocrine therapy, monoclonal antibodies therapy, small molecules, immunotherapy and other), number of different regimens, intent of the most recent therapy and line number for metastatic/locally advanced therapy and best response of the most recent therapy will be described. The time from most recent progression to the date of first dose of study medication will be presented in months, it is defined as:

$$(\text{Date of first dose of IMP} - \text{date of most recent progression})/30.4375.$$

The time from most recent progression to first dose of study medication will not be derived for partial or missing dates of most recent progression.

Further therapies after discontinuation of intervention will be listed.

5.5 APPENDIX 5 DATA HANDLING CONVENTIONS

5.5.1 Analysis windows for time points

Analysis windows will not be used in the by-visit analyses and nominal visits as collected on the eCRF will be used for by-visit analyses.

5.5.2 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the worst on-treatment value, analysis according to out-of-range values, PCSAs and NCI grades, and the shift summaries for safety. Unscheduled visits will be excluded from the by-visit summaries, unless the visit is the selected as the baseline visit. Unscheduled body imaging assessments will be used for the derivation of ORR, PFS, DCR and DoR up to and including the first response of PD per RECIST v1.1.

5.5.3 Analysis cut-off date

Analysis COD will be applied when performing an interim or primary analysis or when summarizing data for SRC meetings. The following will be excluded from the analysis:

- Assessments where the date the assessment was performed is after the COD.
- AEs and medications where the start date is after the COD.
- Events that occur after the COD, for example, deaths.

End dates that are after the COD will be set to blank and the relevant event/medication will be set to ongoing.

5.6 APPENDIX 6 TUMOR RESPONSE ASSESSMENT

5.6.1 Evaluation of lesions

Tumors will be evaluated during the study using RECIST v1.1 guideline ([Eisenhauer et al, 2009](#)). At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

5.6.1.1 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 computerized tomography (CT)/magnetic resonance imaging (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.

5.6.1.2 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 exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

5.6.1.3 Bone lesion measurability

- Bone scan, positron emission tomography (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.

5.6.1.4 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 patients 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').

5.6.2 Response criteria

5.6.2.1 Evaluation of target lesions

- **Complete response:** 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:** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive disease:** 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:** 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:** 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.

5.6.2.2 Special Notes on the Assessment of Target Lesions

5.6.2.2.1 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 CR 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.

5.6.2.2.2 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.

5.6.2.2.3 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'.

5.6.3 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.

5.6.3.1 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

5.6.3.1.1 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.

5.6.3.1.2 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 patients 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.

5.6.3.2 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 PR or CR. 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 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 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 fluorodeoxyglucose-PET (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.

5.6.4 Response assessment

5.6.4.1 Time point response

At each protocol specified time point, a response assessment occurs. [Table 21](#) provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, [Table 22](#) is to be used.

Table 21 - Time point response: patients 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	NE	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

Target lesions	Non-target lesions	New lesions	Overall response
PD	Any	Yes or no	NE
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: Stable disease.

Table 22 - Time point response: patients 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; NE: not evaluable; PD: progressive disease.

^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.

5.6.5 Reasons for Responses

Reasons for responses will be included in the analysis datasets and these reasons are outlined below.

If the participant is not on-study for at least 49 days, there is a tumor assessment indicating SD before this time period and the criterion for PD is not met, then the reason for NE may be displayed as “Minimum criteria for SD duration not met”.

If no baseline or post-baseline tumor assessment is available, the reason for NE may be displayed as “No baseline tumor assessment” and “No evaluable post-baseline tumor assessment” respectively, except in the following two situations:

- The participant meets the requirement for a BOR of PD, because the participant died between the first IMP intake and the planned date of the 2nd tumor assessment.
- The participant discontinues study intervention due to clinical/non-radiological progression (as collected in the eCRF) where the BOR will be set to NE and the reason for NE may be displayed as “Clinical/non-radiological progression without evaluable baseline or post-baseline tumor assessment”.

Participants with the reason for NE of “No evaluable post-baseline tumor assessment” would include participants who are lost to follow-up or discontinued from the study for other reasons including for AEs without having any post-baseline radiological assessments.

If the only evaluable assessment has an overall response of PD and the time between the date of first intake of any IMP and the documentation of PD is greater than 17 weeks, then the reason for NE may be displayed as “Documented PD after two or more non-evaluable tumor assessments”.

6 REFERENCES

Cunningham D, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337-45.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-47.

Fuchs CS, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA oncology*. 2018;4(5):e180013.

Gandhi L, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC, KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-92.

Herbst RS, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. *The Lancet*. 2016;387(10027):1540-50.

Storer BE. Design and analysis of phase I clinical trials. *Biometrics*. 1989;45(3):925-37.

Type of Approval (select one) : ☒ **SAP** ☐ **Initiation of Programming SAP**
☐ **SAP Addendum**

Sponsor Name:	Sanofi		
Sponsor Protocol/ CIP ID:	TCD17465	Fortrea Study ID:	000000242752
SAP text filename:	Sanofi TCD17465 eSAP v2.0		
TFL shells filename:	Sanofi TCD17465 TFL template v2.0		
Version:	2.0	Date:	13Jun2023

Fortrea Approval(s):

Jessica Sadler, Lead Statistician

Approval Signature Print Name Date	
---	--

Sponsor Approval(s):

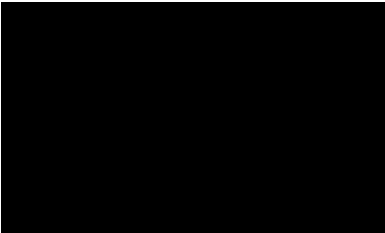
By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Laura Faivre, Lead Statistician**Approval
Signature
Print Name
Date****Keisuke Tada, Statistical****Approval
Signature
Print Name
Date****Nigel Crawford, Global P****Approval
Signature
Print Name
Date**

Certificate Of Completion

Envelope Id: 0457480667DE459CB55946249567D3FC
Subject: Complete with Docusign: Sanofi TCD17465 eSAP v2.0 approval form.pdf
Source Envelope:
Document Pages: 2
Certificate Pages: 5
AutoNav: Enabled
Envelope Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Status: Completed



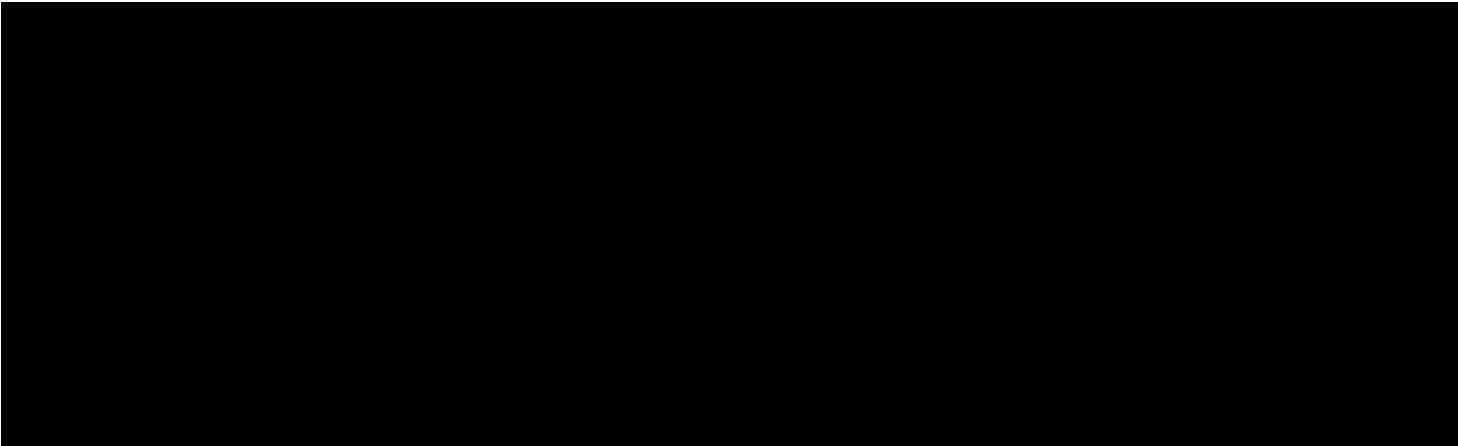
Record Tracking

Status: Original
Holder: [Redacted]
Location: DocuSign

Signer Events

Signature	Timestamp
[Redacted]	

Electronic Record and Signature Disclosure:
Not Offered via DocuSign



Electronic Record and Signature Disclosure:
Accepted: [Redacted]
ID: e6ace22a-96ba-4193-8551-5bcc6e86446a

Signer Events	Signature	Timestamp

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	Status	Timestamp
Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Witness Events	Signature	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	6/13/2024 10:44:48 AM
Certified Delivered	Security Checked	6/13/2024 10:55:24 AM
Signing Complete	Security Checked	6/13/2024 10:55:48 AM
Completed	Security Checked	6/15/2024 11:18:58 AM
Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Fortrea Enterprise (Part 11) (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a \$0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Fortrea Enterprise (Part 11):

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

To advise Fortrea Enterprise (Part 11) of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at privacy@fortrea.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Fortrea Enterprise (Part 11)

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to privacy@fortrea.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Fortrea Enterprise (Part 11)

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

- i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to jay.singleton@labcorp.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: <https://support.docusign.com/guides/signer-guide-signing-system-requirements>.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Fortrea Enterprise (Part 11) as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Fortrea Enterprise (Part 11) during the course of your relationship with Fortrea Enterprise (Part 11).