STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of GS-3583, a FLT3 Agonist Fc Fusion Protein, as Monotherapy and in Combination With Anticancer Therapies in Participants With Advanced Solid Tumors
Name of Test Drug:	GS-3583
Study Number:	GS-US-496-5657
Protocol Version (Date):	Amendment 2 (14 April 2022)
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ADA	anti-drug antibody
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under curve
BICR	blinded independent central review
BLQ	below the limit of quantitation
BMI	body mass index
BoR	best overall response
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRF	case report form
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
EOT	end of treatment
FAS	Full Analysis Set
Hb	hemoglobin
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IRR	infusion-related reactions
ITT	intent to treat
LTT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease

PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	Participant reported outcome
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	recommended Phase 2 dose
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
SD	Stable Disease
SE	standard error
StD	standard deviation
SI (units)	international system of units
SOC	system organ class
SRT	safety review team
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum quantifiable concentration of the drug
C_{tau}	observed drug concentration at the end of the dosing interval
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{max}	time (observed time point) of C_{max}

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and defines key elements including variable definitions for analysis of data of Study GS-US-496-5657 in support of the clinical study report (CSR). This SAP is based on the study protocol Amendment 2 dated 14 April 2022. Any changes made after the finalization of the SAP will be documented in the CSR.

Since the study was terminated prematurely and no participants were enrolled in Part 2, the analysis methods and the key elements for data analysis outlined in this SAP will solely pertain to Part 1. Analysis methods specified in this document take precedence over those described in protocol should there be any difference.

1.1. Study Objectives and Endpoints

Primary Objective(s)	Primary Endpoint(s)
Safety	
Part 1 • To characterize the safety and tolerability of GS-3583 as monotherapy in participants with advanced solid tumors • To determine the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of GS-3583 as monotherapy in participants with advanced solid Tumors	Part 1 • Incidence of dose limiting toxicities (DLTs) • Incidence of AEs and laboratory abnormalities
Part 2 • To assess the safety and tolerability and to determine the RP2D of GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) or in combination with docetaxel in participants with NSCLC (Cohort B)	Part 2 • Incidence of DLTs • Incidence of AEs and laboratory abnormalities
Secondary Objective(s)	**Secondary Endpoint(s)**
Efficacy/Safety/PK delineate objectives and endpoints as appropriate.	
Part 1 • To characterize the PK of GS-3583 as monotherapy in participants with advanced solid tumors • To evaluate the immunogenicity of GS-3583 as monotherapy in participants with advanced solid tumors	Part 1 • GS-3583 PK parameters (Cmax, Tmax, and AUC) Rate of GS-3583 antidrug antibody (ADA)
Part 2 • To evaluate the investigator-assessed confirmed objective response rate (ORR) with GS-3583 in	Part 2 • Confirmed ORR is defined as the percentage of participants who have achieved confirmed CR or

Primary Objective(s)	Primary Endpoint(s)
combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) or in combination with docetaxel in participants with NSCLC (Cohort B) • To assess the preliminary efficacy of GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy versus zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy alone in participants with HNSCC (Cohort A) or in combination with docetaxel versus docetaxel alone in participants with NSCLC (Cohort B) as determined by PFS, duration of response (DOR), and OS • To evaluate investigator-assessed disease control rate (DCR) with GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) or in combination with docetaxel in participants with NSCLC (Cohort B) • To evaluate the PK of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) or in combination with docetaxel in participants with NSCLC (Cohort B) • To evaluate the immunogenicity of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) or in combination with docetaxel in participants with NSCLC (Cohort B)	confirmed PR according to RECIST V1.1 and assessed by the investigator. • Progression-free survival is the time from date of randomization until disease progression or death from any cause, whichever comes first as measured per RECIST V1.1 as assessed by the investigator • Duration of response is measured from the time of first response (CR or PR) identified by RECIST V1.1 as assessed by the investigator until the date of first documented disease progression or death, whichever comes first. • Overall survival is the length of time from date of randomization until the date of death from any cause. • Disease control rate is measured by the percentage of participants with a best overall confirmed response of complete response (CR) or partial response (PR) or stable disease. • PK parameters (Cmax, Tmax, and AUC) for GS-3583 • Rate of GS-3583 ADA
Exploratory Objective(s)	**Exploratory Endpoint(s)**
[redacted]	

Primary Objective(s)	Primary Endpoint(s)
correlation with clinical response in participants with advanced solid tumors	• Time to response (TTR), defined as the interval from start of treatment to the first documentation of CR or PR that is subsequently confirmed
Part 2 • To evaluate the pharmacodynamics of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) or in combination with docetaxel in participants with NSCLC (Cohort B) in blood and tumor samples • To evaluate the PK of zimberelimab administrated in combination with GS-3583 and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) • To evaluate the immunogenicity of zimberelimab administrated in combination with GS-3583 and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in participants with HNSCC (Cohort A) • To explore biomarkers that may predict activity or response to GS-3583	• Overall survival (OS), defined as the time from the first dose date of GS-3583 to death from any cause • Changes in pharmacodynamic markers of GS-3583 (eg, changes in the number of cDC1s, cDC2s, plasmacytoid DCs and other cell types as determined by flow, IHC, imaging, or RNA sequencing) • Other PK parameters of interest, if applicable • Correlations between GS-3583 PK and pharmacodynamics Part 2 • Changes in pharmacodynamic markers of GS-3583 (eg, changes in the number of cDC1s, cDC2s, plasmacytoid DCs and other cell types as determined by flow, IHC, imaging, or RNA sequencing) in blood and tumor tissue • PK parameters (Cmax, Tmax, and Ctrough) for zimberelimab • Rate of zimberelimab ADA • Baseline levels of GS-3583 biomarkers (eg, number of cDC1s, cDC2s, plasmacytoid DCs, and other cell types, gene expression levels, and cytokine levels as determined by flow, IHC, imaging, enzyme-linked immunosorbent assay, or RNA sequencing at baseline) in blood and tumor tissue

1.2. Study Design

Part 1 is a Phase 1b, open-label study to evaluate the safety, tolerability, PK, and preliminary efficacy of GS-3583 in adult participants with advanced solid tumors to determine the MTD or RP2D level of GS-3583 as monotherapy.

Dose escalation will proceed using a standard 3 + 3 design. Doses of 675 µg, 2000 µg, 6000 µg, 12,000 µg, and 20,000 µg are planned. GS-3583 will be administered on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 4-week/28-day cycle for up to 13 cycles or until the participant meets study treatment discontinuation criteria.

The safety and tolerability of each dose level will be assessed by the safety review team (SRT) after all participants in the cohort have had 2 doses of GS-3583 and have been followed for at

least 28 days after the first dose of GS-3583 or if participants had DLTs during the first 28 days of study drug dosing.

The initial block of each dose consists of 3 participants. Dose escalation will occur if no participants experience a DLT during the first 28 days of study drug dosing. If 1 participant within the initial cohort of 3 participants experiences a DLT during the first 28 days of study drug dosing, an additional 3 participants will be enrolled at the same dose level. If no DLTs are observed in the additional 3 participants, dose escalation will occur. If 2 or more participants experience DLTs within the first 28 days, dose de-escalation to a lower dose will occur. The MTD is the highest dose level with a participant incidence of DLTs of < 33% in 6 or more participants during the first 28 days of study drug dosing. A minimum of 6 participants need to be treated at a dose level before this dose level can be deemed as the MTD. A participant who fails to receive all GS-3583 treatments or fails to complete all safety assessments in the DLT period for reasons other than DLT will be replaced.

The SRT will review safety and relevant clinical data and make the dose escalation/stay/de-escalation decision. Source data verification is not required to be performed prior to SRT meetings, as there will be alternative quality control checks implemented. These checks will be described in the safety review team charter. The SRT may also add up to 6 additional participants to any cohort determined to be safe to collect additional safety and PK/pharmacodynamic information. The SRT may also designate intermediate dose levels in addition to the ones listed in protocol after reviewing all the available safety and PK/pharmacodynamic information.

The dose of GS-3583 taken forward for Part 2 in combination with other anticancer agents will be determined based on all relevant clinical data from all participants treated in the dose-escalation phase. This dose will not exceed the MTD.

Part 2 is a Phase 1b, open-label, multicenter study evaluating GS-3583 in combination with other anticancer therapies. There will be 2 cohorts in Part 2, each comprising safety run-in and open-label randomized expansion phases. Each safety run-in cohort will enroll 6 to 18 participants based on observed toxicities. Once the SRT reviews each safety run-in cohort and the sponsor determines the RP2D for that cohort, randomized expansion cohorts will be enrolled (each randomized expansion cohort may commence enrollment based on the results of the corresponding safety run-in cohort). Up to 45 participants will be randomized 2:1 to treatment and control arms in each randomized expansion cohort.

An overview of the study design for Part 2 is shown in Figure 1-1 and Figure 1-2.

Figure 1-1. Part 2 Study Schema

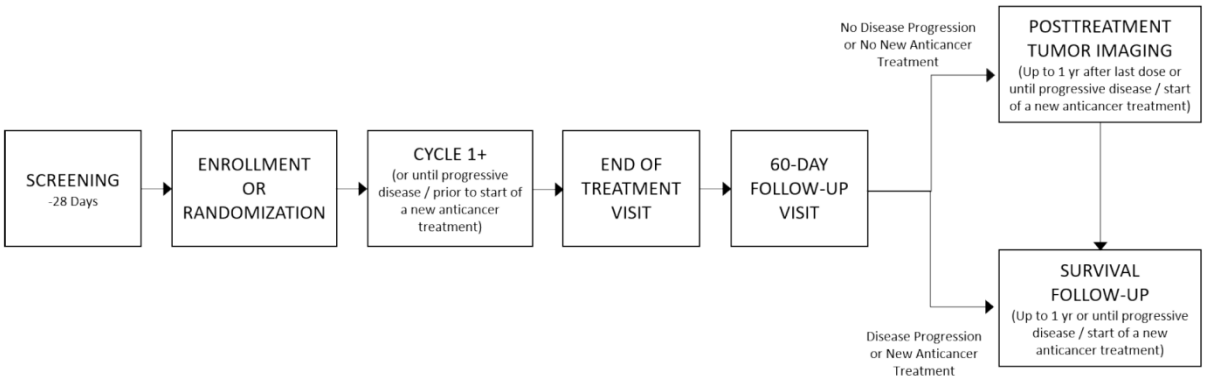
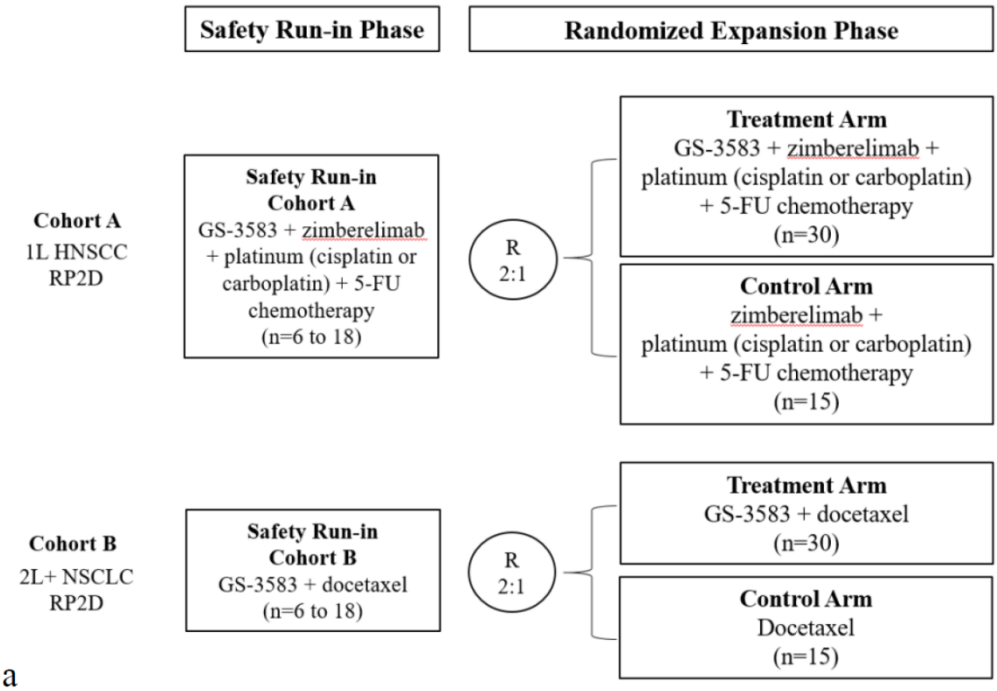


Figure 1-2. Part 2 Safety Run-in and Randomized Expansion Phases



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5-FU = 5-fluorouracil; HNSCC = head and neck squamous cell carcinoma; NSCLC = non–small-cell lung cancer; RP2D = recommended Phase 2 dose

1.3. Sample Size and Power

A total of approximately 150 participants will be enrolled.

For Part 1, assuming up to 4 planned dose levels will be tested with 3 DLT-evaluable participants for the first dose level and up to 6 DLT-evaluable participants per subsequent dose

level, 21 DLT-evaluable participants will be needed. Assuming 10% are not evaluable, approximately 24 participants will be enrolled in Part 1.

For Part 2, a maximum of 63 participants will be enrolled for each cohort. Six to 18 participants will be evaluated in Safety Run-in Cohorts, and 45 participants will be enrolled in Randomization Expansion Cohorts with 2:1 randomization ratio. The total maximum sample size in Part 2 is approximately 126.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Part 1 Dose-Escalation Analysis and Part 2 Safety Run-in Analysis

For the purpose of making the decision whether to escalate to the next dose level/cohort, interim analyses of relevant safety and available PK data will be conducted by Gilead after all participants in each cohort have completed dosing and the follow-up period in the DLT period as defined in protocol. Safety assessments (eg, AEs, ECG, and laboratory results) will be displayed by cohort or dose level to facilitate the decision.

2.2. Final Analysis

The final analysis will be performed after all participants have completed or discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

3.1. Analysis Sets

A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all participants who received a study participant identification number in the study after screening.

The All Enrolled Analysis Set will be used for data listings, unless otherwise specified.

3.1.2. DLT Evaluable Analysis Set

The DLT Evaluable Analysis Set includes all participants who were enrolled for dose escalation, received all prescribed treatments and completed safety procedures through DLT assessment period (from Day 1 through Day 28 inclusive of the last day) or experienced a DLT prior to end of DLT assessment period as specified in protocol. Determination of MTD or RP2D will be based on the DLT Evaluable Analysis Set.

3.1.3. Safety Analysis Set

The Safety Analysis Set will include all participants who received at least 1 dose of study drug. This will be the primary analysis set for safety analysis.

3.1.4. Full Analysis Set

The Full Analysis Set includes all enrolled participants who received at least 1 dose of study drug (Part 1 and Part 2 Safety Run-in Cohorts) or all randomized participants (Part 2 Randomized Expansion Cohorts). This will be the primary analysis set for efficacy analyses.

3.1.5. Pharmacokinetic Analysis Set

The PK Analysis Set includes all enrolled participants who received at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This will be the primary analysis set for all PK analyses.

3.1.6. Immunogenicity Analysis Set

Immunogenicity Analysis Set will include all enrolled participants who received at least 1 dose of study drug and have at least 1 nonmissing ADA test result. This is the primary analysis set for immunogenicity data analyses.

3.1.7. Biomarker Analysis Set

The Biomarker Analysis Set will include all enrolled participants who received any study drug and have at least 1 evaluable post-baseline biomarker measurement available.

3.2. Participant Grouping

For analyses based on the Full Analysis Set, participants will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, DLT Evaluable Analysis Set and PK Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the assigned treatment only when their actual treatment differs from assigned treatment for the entire treatment duration.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling participants. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroupings for efficacy and safety analyses.

3.5. Adjustment for Multiplicity

CCI [redacted]

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

3.6.2. Outliers

Outlier values in non-PK data will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.
- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing concentrations and PK parameters in intensive PK samples. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes.

The following conventions will be used for the presentation of summary and order statistics for intensive PK concentrations:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. The following special situations due to COVID-19 will be handled in the analysis:

- Study treatment or study discontinuation due to COVID-19
- Protocol deviations due to COVID-19
- Missed and Virtual Visits due to COVID-19
- Adverse events due to COVID-19
- Death due to COVID-19

4. PROTOCOL DEVIATIONS

Participants who did not meet the eligibility criteria for study entry, but enrolled in the study will be identified regardless of whether they were exempted by the sponsor or not. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. Important protocol deviations will be listed by participant for All Enrolled Analysis Set.

5. PARTICIPANT INFORMATION

5.1. Participant Enrollment and Disposition

Key study dates (i.e.,first participant screened, first participant enrolled, last participant enrolled, last participant last visit for the primary endpoint, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided by treatment group for each investigator within a country and overall.

A summary of participant disposition will be provided by treatment group based on the All Enrolled Analysis Set. This summary will present the number of participants screened and the number of participants in each of the categories listed below:

- Safety Analysis Set
- DLT Evaluable Analysis Set
- Full Analysis Set
- Pharmacokinetic Analysis Set
- Immunogenicity Analysis Set
- Discontinued study drug with reasons for discontinuation of study drug
- Discontinued the study with reasons for discontinuation of study

5.2. Extent of Study Treatment Exposure

Extent of exposure to study treatment will be summarized using descriptive statistics for total duration of exposure to each study drug, total number of doses received, total number of cycles and total cumulative dose administered.

Duration of treatment (in days) will be calculated as (the last dose date - the first dose date + 1). Cumulative dosage (mg/kg) received for each participant is defined as the sum of all delivered dosages (mg/kg) of all infusions the participant received in the study.

5.3. Demographics and Baseline characteristics

Participant demographics and baseline characteristics will be summarized with descriptive statistics by treatment arm for Safety Analysis Set, which include

- Age

- Gender
- Race
- Ethnicity
- Weight
- Height
- Body mass index (BMI)
- ECOG status

5.4. Medical History

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

Disease-specific medical history including disease-specific prior anticancer therapies and radiotherapy will be listed by participant.

5.5. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

5.5.1. Prior Medications

Prior medications are defined as any medications taken before a participant took the first study drug. Prior medication data will be reported by a by-participant listing only.

5.5.2. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study treatment. For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study treatment and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study treatment will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study treatment will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study treatment or a start date after the last dosing date of study treatment will not be considered as concomitant medications. Medications with partially or completely missing start and stop dates will be considered concomitant medication, unless the partial missing date suggested otherwise.

Concomitant medication data will be reported by a by-participant listing only.

5.6. Post Treatment Anti-cancer Therapies

All post treatment anti-cancer therapies (other than those allowed per-protocol) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

6. EFFICACY ANALYSES

6.1. Efficacy Endpoints

6.1.1. Definition of the Efficacy Endpoints

Best overall response (BoR)

Best overall response (BoR) is calculated based on the overall visit responses from each RECIST assessment including unscheduled visits. It is the best response a participant has had from the start of treatment until objective documentation of PD (per RECIST v1.1 in Appendix 1), or participant withdrawn from the study, or participant started new anticancer therapy, whichever occurs first. Categorization of BoR will be based on RECIST v1.1 using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Not Evaluable (NE).

A BoR of CR or PR must be confirmed. A CR/PR requires confirmation no less than 4 weeks (28 days) after the first response criterion was met and with no evidence of progression between the initial and CR/PR confirmation visit. Participants who responded with an unconfirmed CR/PR at the time of data cutoff will be reported as unconfirmed CR/PR under the SD category provided the minimum criteria for SD duration are met, otherwise this will be reported under the NE category.

For determination of a BoR of SD, the earliest timepoint SD can be recorded will be at the time of the first scheduled scan (8 weeks) minus any applicable window (minus 1 week) after the first dosing date. For the determination of BoR, an overall visit response with “Non-CR/non PD” is considered as SD.

For participants who die with no evaluable RECIST assessments, if the death occurs ≤9 weeks (i.e. 8 weeks + 1 week to allow for a late assessment within the assessment window) after the first dosing date, then BoR will be assigned to the progression (PD) category. For participants who die with no evaluable RECIST assessments, if the death occurs > 9 weeks after the first dosing date then BoR will be assigned to the NE category.

Objective response rate (ORR)

ORR is defined as the proportion of all enrolled participants who achieve the best overall response of CR or PR as determined by investigator. Tumor response assessments after the date of participants receiving new anticancer therapy will be excluded from the analysis. The response definition of each response category is based on RECIST 1.1. Participants who do not have baseline or on-study response status assessment or received new anticancer therapy prior to achieving CR or PR, will be considered as non-responders.

Progression-free survival (PFS)

PFS is defined as the interval from the first dosing date of study treatment to the earlier date of the first documentation of objective disease progression by investigator or death from any cause. Disease progression is determined based on RECIST 1.1, as defined in protocol Appendix 7.

PFS in months = (Date of event/censoring – Date of first dosing date + 1)/30.4375.

Table6-1. Rule for PFS Calculation

Situation	Outcome	Date of Event/Censoring
No disease assessment at baseline or post-baseline*	Censored	Date of first dosing date
No documented PD or death	Censored	Date of last evaluable disease assessment
Documented PD	Event	Date of first documented PD
Death without any documented PD	Event	Date of death
Death within 2 disease assessments window and no baseline or post-baseline assessment	Event	Date of death
PD or death after ≥ 2 consecutively missed or NE disease assessments	Censored	Date of last evaluable assessment prior to missed or NE assessments
Subsequent anticancer therapy initiated prior to PD or death	Censored	Date of last evaluable assessment prior to subsequent anticancer therapy

*Baseline tumor assessment should be performed no more than 28 days before the start of study drug.

Duration of response (DOR)

DOR is defined for confirmed responders as duration of time from the date of initial response to the date of first documentation of disease progression or the date of death due to any cause, whichever occurs first.

DOR in months = (Date of disease progression/death or censoring – Date of initial response + 1) / 30.4375.

Date of initial response is the date of first response achieved and then confirmed by a subsequent disease assessment conducted prior to or at the initiation of the next line of anticancer therapy.

For responders, DOR will use the PFS censoring time. DOR will not be defined for those participants who do not have documented responses.

Time to response (TTR)

Time to response (TTR) will be summarized with descriptive statistics only for confirmed responders (PR or better) based on disease assessments conducted prior to or at the initiation of the next line of anticancer therapy.

TTR will be calculated as the time from the first dosing date of study treatment to date of first documented response.

TTR in months = (Date of response - date of the first dosing date + 1)/30.4375

Overall survival (OS)

OS is defined as the interval from first dosing date of study treatment to death from any cause. For participants who were not known to have died at the time of the analysis, OS data will be censored at the last date that they were known to be alive. In the event that the participant has withdrawn consent, the vital status of the participant can be obtained by site personnel from publicly available resources under applicable local laws.

OS in months = (date of event/censoring – date of first dose of study drug + 1) / 30.4375.

Disease Control Rate (DCR)

DCR is defined as the proportion of participants with best response of CR, PR, or SD.

Change from Baseline in Tumor Lesions

For participants with solid tumors, the percent change from baseline in the sum of diameters of target lesions as documented radiographically will be determined for each postbaseline assessment. The baseline sum of the diameters will be the value of last target lesion assessment prior to the start of treatment.

Waterfall plots for the percent change from baseline in the sum of diameters of target lesions for BoR of each individual participant will be generated.

The details of tumor lesion assessments by visit will be listed by cohort and participant ID number in ascending order, including target and non-target lesions, any new lesions, percent change from baseline, and percent change from nadir in sum of diameters of target lesions.

6.1.2. Analysis of the Efficacy Endpoint

For each treatment arm BoR will be summarized by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analyses are planned for BoR.

ORR and the corresponding 90% confidence intervals based on Clopper-Pearson method of each treatment group will be presented.

DCR along with the 2-sided 90% exact CIs (using the same methods as for ORR) will be presented.

By-participant listings of objective response, DOR, TTR, PFS and OS will be provided by participant ID number in ascending order.

6.2. Changes From Protocol-Specified Efficacy Analyses

Due to the early termination of the study, analyses on PFS, DOR and OS using Kaplan-Meier (KM) method specified in the protocol will not be included in the analysis plan. No analyses will be done for cohorts after Cohort 5.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 5.0.

7.1.3. Relationship of Adverse Events to Study Treatment

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any events not present prior to the study treatment, or any events already present but worsening in either intensity or frequency following exposure to the study treatment.

The TEAE reporting period is defined as the period from the date of the first dose of study treatment up to 90 days after the date of the last dose of study treatment or the day before initiation of subsequent therapy, whichever comes first.

7.1.5.2. Missing or incomplete Dates

If there was a missing or incomplete date for the start date or stop date of an AE, the most conservative approach was used for analysis. An AE with a complete missing onset date but a resolution date after initiation of study treatment will be considered treatment-emergent unless the incomplete date suggested otherwise.

7.1.6. Summaries of Adverse Events and Deaths

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group:

- TEAEs
- TEAEs by maximum severity

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs by maximum severity
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE AEs leading to death

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs and TE SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths

A summary (number and percentage of participants) of deaths will be provided by treatment group. Summary will include the following categories:

- All deaths
- Deaths within 90 days of the last dosing of study treatment
- Deaths beyond 90 days of the last dosing of study treatment

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity (DLT)

For each cohort being evaluated for safety and tolerability based on DLT assessment, DLT evaluable participants are identified as those who were enrolled for dose escalation, either experienced a DLT any time during the DLT assessment period or completed all treatments of study drug and completed safety procedures during the DLT assessment period.

A listing of the DLT AEs will be provided by cohort including cohort number with dose level, participant identification, actual dose amount prior to or on the start date of the AE, DLT term from investigator as well as CTCAE term and associated severity grade, if available.

7.1.7.2. Infusion-related Reactions (IRR)

Infusion-related reactions will be collected on the CRF. A listing of IRR AEs will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected during the treatment-emergent period. The analysis will be based on values reported in conventional units.

7.2.1. Summaries of Numeric Laboratory Results

Spaghetti plots for white blood cells and monocytes of individual participants will be provided. By-participant listings of results of laboratory tests will be provided for All Enrolled Analysis Set by participant ID number and visit in chronological order.

7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point up to 90 days after the date of the last dose of study treatment or the day before initiation of subsequent therapy, whichever comes first. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 2 toxicity grades at any postbaseline time point during treatment-emergent period. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and dose cohort within each treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- laboratory abnormalities (Grade 1 to 4 separately)
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants in the safety analysis set. By-participant listings will be provided for treatment-emergent laboratory abnormalities and Grade 3 or 4 laboratory abnormalities by participant ID number in chronological order.

7.3. Body Weight and Vital Signs

A by-participant listing will be provided for body weight, height, BMI, blood pressure, heart rate, temperature, and respiratory rate by participant ID number in chronological order.

7.4. Electrocardiogram Results

A by-participant listing will be provided for electrocardiogram results by participant ID number in chronological order.

7.5. Other Safety Measures

7.5.1. Echocardiogram

A by-participant listing will be provided for echocardiogram and multigated acquisition (MUGA) scan results by participant ID number in chronological order.

7.5.2. Surgeries and Procedures

A by-participant listing will be provided for prior and on-study surgeries and procedures by participant ID number in chronological order.

7.6. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) AND IMMUNOGENICITY ANALYSES

8.1. PK Sample Collection

Blood sample collection for GS-3583 PK characterization will be conducted at protocol specified time points.

Part 1:

At Cycles 1 and 3, blood will be collected at predose (< 30 minutes before start of infusion), end of infusion (+ 5 minutes), and 2 hours (± 10 minutes), 6 hours (± 0.5 hours), Day 2 (24 hours [± 2 hours]), Day 3 (48 hours [± 4 hours]), Day 5 (96 hours [± 4 hours]), Day 8 (168 hours [± 12 hours]), Day 15 (for Cycle 1: pre-Day 15 dose [< 30 minutes before start of infusion], end of Day 15 infusion (+ 5 minutes), and 2 hours after start of Day 15 infusion (± 10 minutes); for Cycle 3: 336 hours [± 12 hours]), and Day 24 (552 hours [± 12 hours]) after start of the Day 1 infusion.

In addition, samples will be collected on Day 1 (predose), and Day 15 (336 hours) of Cycles 2, 4, and every subsequent even numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the end of treatment (EOT) visit if a participant terminates early from study treatment.

Part 2 Cohorts A and B

GS-3583 (Safety Run-in Cohorts): At Cycles 1 and 3, blood samples will be collected at predose (≤ 30 minutes before start of infusion), end of infusion (+ 5 minutes), and 2 hours (± 10 minutes), 6 hours (± 0.5 hours), Day 8 (168 hours [± 12 hours]), and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion.

In addition, blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 2, 5, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a participant terminates early from study treatment.

GS-3583 (Randomized Expansion Cohorts Treatment Arms): Blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 1, 2, 3, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a participant terminates early from study treatment.

Part 2 Cohort A

Zimberelimab (Safety Run-in Cohort and Randomized Expansion Cohort Control and Treatment Arms): Blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 1, 2, 3, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a participant terminates early from study treatment.

8.2. PK Analyses Related to Intensive PK Sampling

8.2.1. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to zero.

For area under the curve (AUC), samples that are BLQ of the bioanalytical assays occurring prior to the attainment of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{inf}, λ_z, and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of the drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. PK Parameters

PK parameters will be generated for all participants in the PK Analysis Set. The analytes and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study. The primary PK parameters are [AUC_{last}, AUC_{tau}, and C_{max}] of GS-3583. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-1. PK Parameters for Each Analyte

Analyte	Parameters
GS-3583	AUC_{tau} (AUC_{0-15}, AUC_{0-28}), C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, C_{max}/Dose, AUC_{tau}/Dose

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter.

8.3. Immunogenicity analysis

The immunogenicity analyses will use the Immunogenicity Analyses Set. The following measures of anti GS-3583 antibody positivity will be reported: ADA prevalence rate, ADA incidence rate (i.e. sum of Treatment-Induced and Treatment-Boosted ADA rate), ADA transience/persistence rate, and anti-body prevalence rate.

ADA Prevalence Rate: the proportion of participants who had at least one positive ADA sample based on the Immunogenicity Analysis Set.

Treatment-Boosted ADA Rate: the proportion of participants who had positive baseline ADA sample and at least one positive post-treatment ADA sample and the (max titer of the posttreatment ADA) / (titer of baseline ADA) >= 9 based on the Immunogenicity Analyses Set.

Treatment-Induced ADA Rate: the proportion of participants who had negative baseline ADA sample and at least one positive post-treatment ADA sample based on participants who had both non-missing baseline and at least one post-treatment ADA result reported.

ADA incidence (treatment-emergent ADA): is the sum of both treatment-induced and treatment boosted ADA-positive participants as a proportion of the evaluable participant population.

Transient ADA is defined as: a) Treatment-Induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time). or

b) Treatment-Induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive sample (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the participant's last sampling time point is ADA-negative.

ADA Transience Rate: the proportion of participants who had transient ADA based on the Immunogenicity Analyses Set.

Persistent ADA is defined as a) Treatment-Induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive sample (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer. or b) Treatment-Induced ADA only in the last sampling time point of the treatment study period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

ADA Persistence Rate: the proportion of participants who had persistent ADA based on the Immunogenicity Analyses Set.

The following ADA categories will be summarized by treatment arms.

- ADA prevalence
- ADA positive post-baseline and positive at baseline
- ADA not detected post-baseline and positive at baseline
- ADA incidence
- Treatment-induced ADA
- Treatment-boosted ADA
- Persistent ADA
- Transient ADA

ADA titers and positive ADA values will be summarized by visits and treatment arms. A by-participant listing for ADA status at each time point, along with treatment, visit, ADA sample collection status, reason of sample not collected, ADA result, and titer for participants with positive ADA status will be provided by participant ID number and time point in chronological order.

9. BIOMARKER ANALYSIS

Biomarker analyses will be described in the biomarker analysis plan.

10. REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eur J Cancer 2009;45 (2):228-47.

11. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

13. APPENDIX 1 RECIST 1.1-BASED ASSESSMENTS - OVERALL VISIT RESPONSE

The RECIST tumor response data will be used to determine each participant's visit response according to RECIST version 1.1. At each visit, participants will be assigned a RECIST 1.1 visit response of CR, PR, SD or PD, using the information from TLs, non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a participant has had a tumor assessment which cannot be evaluated, then the participant will be assigned a visit response of NE. For participants with no disease at baseline (i.e. no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be no evidence of disease (NED). If a new lesion is observed then the overall visit response will be PD. **Table A2-13-1** summarizes overall visit response given the visit responses from TL and NTL are combined with new lesion.

Table A2-13-1. Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR or NA	No	CR
CR	Non CR/Non PD or NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NE	Non PD or NE or NA	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NA	CR	No	CR
NA	Non CR/Non PD	No	SD
NA	NE	No	NE
NA	NA	No	NED

CR Complete response, NA Not applicable, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NED No evidence of disease.

SAP GS-US-496-5657

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	15-Jun-2023 15:05:55
PPD	Biostatistics eSigned	15-Jun-2023 21:58:49