Statistical Analysis Plan

Title: Statistical Analysis Plan for Protocol SL03-OHD-102: Phase 1 Dose Escalation Study of the Agonist Redirected Checkpoint, SL-172154 (SIRPα-Fc-CD40L), Administered Intratumorally in Subjects with Cutaneous Squamous Cell Carcinoma or Squamous Cell Carcinoma of the Head and Neck

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LIST OF ABBREVIATIONS

Ab	Antibody
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARC	Agonist redirected checkpoint
AST	Aspartate aminotransferase
AUC	Area under the serum concentration time curve
AUC0-last	Area under the serum concentration time curve, time 0 to the last quantifiable concentration
AUC0-inf	Area under the serum concentration time curve from time 0 extrapolated to infinity
AUC0-t	Area under the serum concentration time curve, time 0 to time = t
%AUCext	Percentage of AUC0-inf due to extrapolation from Tlast to infinity
AUCtau	The area under the serum concentration time curve, over the dosing interval
β-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
°C	Degrees Celsius
CBC	Complete blood count
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
C1D1	Cycle 1, day 1
CL	Clearance
Cm	Centimeters
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CO2	Bicarbonate
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRS	Cytokine release syndrome
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
DAT	Direct antiglobulin test
DC	Dendritic cells
DLT(s)	Dose-limiting toxicity(ies)
DOR	Duration of response
ECD	Extracellular domain
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of injection(s)
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FP	Fusion protein

FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HNSCC	Head and neck squamous cell carcinoma
hr (time)	Hour(s)
HR	Heart rate
HSR(s)	Hypersensitivity reaction(s)
IB	Investigator brochure
ICF	Informed consent
ICH	International Conference of Harmonisation
IEC	Institutional Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
irAE	Immune-related adverse event
irSAE	Immune-related serious adverse event
ISR	Injection site reactions
ITI	Intratumoral injection
itRECIST	Intratumoral response evaluation criteria in solid tumors
IV	Intravenous or intravenously
Kg	Kilogram
LDH	Lactate dehydrogenase
mAb(s)	Monoclonal antibody(ies)
MABEL	Minimum anticipated biological effect level
MAD	Maximum administered dose
mg	Milligrams
mg/dL	Milligrams per deciliter
mg/kg	Milligrams per kilogram
Min	Minutes
mL	milliliter
mm	millimeter
Mmol	Millimole
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval 2
NCI	National Cancer Institute
Ng	Nanogram
NK	Natural killer
nM	Nanomolar
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive Disease

PD-1	Programmed cell death protein 1
PD-L1 / PD-L2	Programmed cell death ligand 1 / Programmed cell death ligand 2
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
pM	Picomolar
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RR	Respiratory rate
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SCCIS	Squamous cell carcinoma in situ
SD	Stable disease
SL-172154	SIRPα-Fc-CD40L agonist redirected checkpoint
SMC	Safety Monitoring Committee
SOA	Schedule of Assessments
SPM	Study Pharmacy Manual
SUSAR	Suspected, unexpected serious adverse reaction
T	Temperature
T4	Thyroxine 4
t½	terminal elimination half-life
SIRPα	Signal regulatory protein alpha
TK	Toxicokinetic
Tlast	Time of last observed quantifiable concentration
Tmax	Time of maximum observed concentration
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
TTR	Time to tumor response
TXT	Treatment
µg	Microgram
ULN	Upper limit of normal
Vz	Volume of distribution
WBC	White blood cell
Wk	Week
λz	Terminal elimination rate constant
~	Approximately
º	Degree

1. INTRODUCTION

This statistical analysis plan outlines the planned analyses for Protocol SL03-OHD-102: Phase 1 Dose Escalation Study of the Agonist Redirected Checkpoint, SL-172154 (SIRPα-Fc-CD40L), Administered Intratumorally in Subjects with Cutaneous Squamous Cell Carcinoma or Squamous Cell Carcinoma of the Head and Neck:

Protocol Version	Approval date
Version v0.0	28May2020
Version v1.0	10July 2020

The purpose of this analysis plan is to provide specific guidelines from which the analysis of this study will proceed. As of 24February2022, the study enrollment was prematurely discontinued. This SAP is updated to reflect the changes in the data analysis due to the premature discontinuation of the study.

All decisions regarding data analysis, as defined in this document, have been made prior to Database Freeze of the study data. Any deviations from these guidelines will be documented in the clinical study report.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Objective	**Outcome Measure**
Primary Objectives	
To evaluate the safety and tolerability of ITI administration of SL-172154 and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of SL-172154	Safety/tolerability outcomes include: incidence of all adverse events (AEs) and immune-related adverse events (irAE), serious adverse events (SAEs), fatal SAEs, dose limiting toxicity (DLT), AEs and irAEs leading to discontinuation, and changes in safety assessments (e.g., laboratory parameters, vital signs etc.) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE – version 5.0). The MTD is defined based on the rate of DLTs and the MAD is the highest dose administered.
Secondary Objectives	
To select the recommended Phase 2 dose (RP2D) for SL-172154 when administered by intratumoral injection (ITI)	Based on review of all data collected during dose escalation and the pharmacodynamic cohort including safety, tolerability, PK, anti-tumor activity, and pharmacodynamic effects.
To assess preliminary evidence of anti-tumor activity of SL-172154 when administered by ITI	Response per investigator assessment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

	▪ Objective response rate (ORR) (proportion of subjects whose best response is a complete response [CR] or partial response [PR]) ▪ Time to response (TTR): time from the first dose until the first response (CR or PR, whichever is recorded first) that is subsequently confirmed ▪ Duration of response (DOR): time between first response (CR or PR, whichever is recorded first) that is subsequently confirmed and date of disease progression ▪ Change from baseline lesion diameter for injected lesion ▪ Change from baseline lesion diameter for non-injected lesion
To evaluate anti-drug antibodies (ADA) to SL-172154 when administered by ITI during and after treatment.	▪ Number/proportion of subjects with positive ADA titer ▪ ADA duration ▪ Transient vs. persistent ADA
To characterize the pharmacokinetics (PK) of SL-172154 when administered by ITI	▪ Maximum observed concentration (Cmax) and time at which the maximum concentration is observed (Tmax) and minimum observed concentration (Cmin) following single and multiple doses of SL-172154 ▪ Area under the serum concentration-time curve (AUC) ▪ Terminal elimination half-life ($t_{1/2}$), Clearance (CL) and Volume of Distribution (Vz).
Exploratory Objectives	
To assess pharmacodynamic biomarkers in blood prior to, on-treatment and following SL-172154 when administered by ITI	Pharmacodynamic biomarkers in blood may include: ▪ Changes from baseline in cell counts and percentages of circulating immune cells such as: T cells, B cells, natural killer (NK) cells, and myeloid cells ▪ Circulating chemokine and cytokine levels
To assess pharmacodynamic biomarkers in tumor tissue prior to, on-treatment and following SL-172154 when administered by ITI	Pharmacodynamic biomarkers in tumor tissue may include: ▪ Presence of SL-172154 in tumor tissue

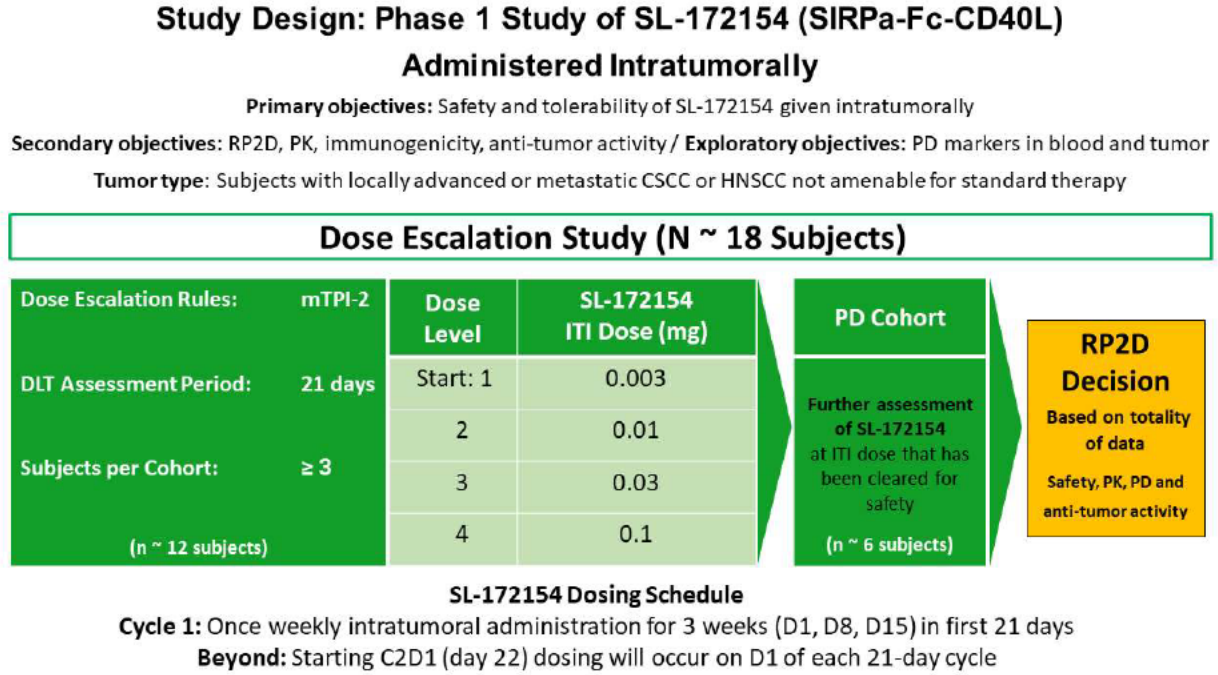
	▪ Changes in T cells subsets, B cells and macrophages and assessment of SL-172154 in the tumor tissue ▪ CD47 and CD40 expression ▪ Programmed cell death ligand 1 (PD-L1) expression
To estimate progression-free survival (PFS)	▪ PFS: time from first dose to progression by RECIST v1.1 or death, whichever comes first

3. STUDY DESIGN

This clinical trial is an open label, multi-center, dose escalation, Phase 1 study of SL-172154 administered by ITI injection in subjects with Cutaneous Squamous Cell Carcinoma (CSCC) or Squamous Cell Carcinoma of the Head and Neck (SCCHN).

3.1 Study Design

This trial is designed to evaluate the safety, PK, anti-tumor activity and pharmacodynamic effects of SL-172154 administered by ITI on days 1, 8, 15 of a 21-day in cycle 1 and then on day 1 of each subsequent 21-day cycle (cycles ≥ 2). Subjects that are eligible for enrollment have locally advanced or metastatic CSCC or SCCHN that is not amenable to further treatment with surgery, radiation or standard systemic therapies that are known to provide clinical benefit for their condition (see Schema below).



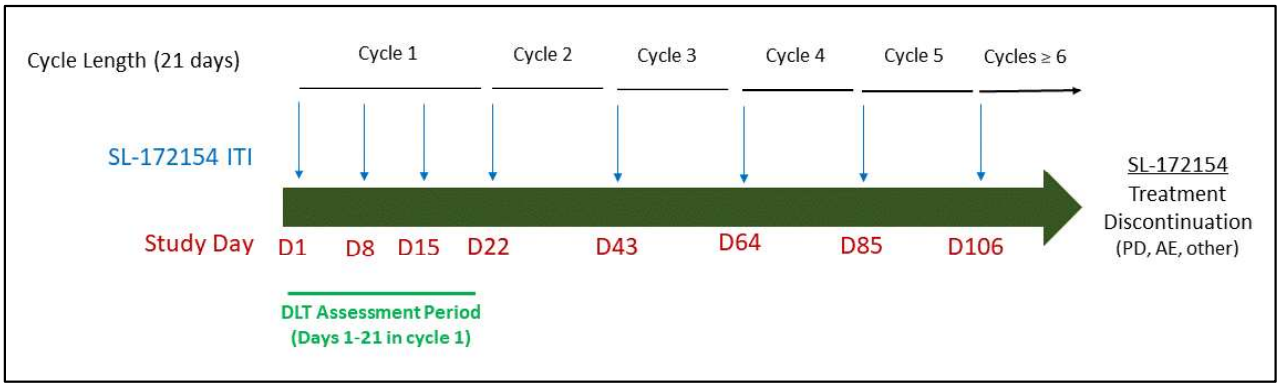
Dose Escalation Cohorts

Dose escalation will utilize the modified Toxicity Probability Interval (mTPI-2) design with target DLT rate of 30% for the MTD as described by Guo et al. Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 and evaluated for DLT during the 21-day DLT evaluation period starting from the first dose of SL-172154. At each dose level, a minimum 3-day stagger between dosing the first and second subject is required. Dose escalation will proceed using a flat dose and fixed volume format with the starting dose of 0.003mg. The planned dose escalation is in half-log increments as outlined in Table 1. The DLT assessment period is 21 days in length and encompass the first 21-day cycle of study treatment. The ITI schedule is outlined in Figure 1.

Table 1: Intratumoral Dose Escalation Plan for SL-172154

Dose Level	ITI Dose (mg) of SL-172154[a]	ITI Volume of Dose
Level 1 - starting dose	0.003	1.5 mL
Level 2	0.01	1.5 mL
Level 3	0.03	1.5 mL
Level 4	0.1	1.5 mL
a) Intermediate or higher dose levels may be tested based on emerging safety and/or pharmacodynamic data. Dose escalation will not exceed half-log increments.		

Figure 1: ITI Schedule for SL-172154



For each dose level, the minimum number of subjects evaluable for DLT (see Section 4**Error! Reference source not found.** for definition of DLT evaluable subject) will be 3 unless unacceptable toxicity is observed prior to enrollment of 3 subjects (e.g., the first 2 subjects experience a DLT before the third subject enrolls). The maximum number of subjects evaluable for DLT at a dose level will be 12 (e.g., this may be reached by sequential enrollment of 4 cohorts of 3 subjects) assuming the dose decision is to stay at the current dose from the first 3 cohorts. Section 3.2 details the statistical design for dose escalation and dose escalation rules.

During dose escalation, a review of available safety data for all subjects will be undertaken by the Safety Monitoring Committee (SMC) approximately every four weeks starting from dosing of the first subject. Decisions will be made based on the safety profile of the current and prior dose levels.

Pharmacodynamic Cohorts

The Sponsor, in consultation with the SMC, may elect to open a pharmacodynamic cohort to obtain additional pharmacodynamic data from approximately 6 additional subjects at one or more dose levels that have completed evaluation for safety without exceeding the MTD. Subjects in the pharmacodynamic cohort must have tumor accessible and safe for biopsy from both an injected lesion and a non-injected lesion and must consent to providing paired biopsies for translational research. Subjects enrolled in the pharmacodynamic cohort will not inform dose escalation decisions but the pharmacodynamic and other data gathered from these additional subjects will inform selection of doses for further evaluation and the RP2D determination.

Selection of the Recommended Phase 2 Dose

Selection of the RP2D for SL-172154 monotherapy will be based upon the totality of the data in subjects treated in dose escalation and pharmacodynamic cohorts. The totality of the data refers to safety, tolerability, PK, clinical activity, and pharmacodynamic markers consistent with the mechanism of action. Approximately 6 subjects (inclusive of the subjects enrolled in the Dose Escalation and Pharmacodynamic cohort) may be treated at the RP2D.

3.2 Statistical Design for Dose Escalation

The dose escalation will utilize a mTPI-2 design with target DLT rate of 30% for the MTD. The mTPI-2 design employs a simple Beta-Binomial Bayesian model with decision rules based on the unit probability mass from the posterior probability of DLT rate. With the target DLT rate of 30%, the posterior probability of DLT rate unit interval (0, 1) is divided into subintervals with equal length of 0.1 that correspond to different dose escalation decisions: subinterval of (0.25, 0.35) is to stay at the current dose, subintervals below 0.25 is to escalate to next higher dose, and subintervals above 0.35 is to de-escalate to the next lower dose. Subjects will be enrolled in cohorts of approximately 3 subjects during the dose escalation. After each cohort of approximately 3 subjects, the posterior unit probability for subintervals will be calculated based on a noninformative prior distribution for the DLT rate (Beta(1,1)) and the total number of subjects with DLTs and DLT evaluable subjects for the current dose. A dose escalation/stay/de-escalation decision that corresponds to the subinterval with the highest unit probability mass will be selected. A minimum of 3 DLT evaluable subjects will be enrolled to a dose level and evaluated for DLT before a dose escalation/stay/de-escalation decision can be made unless unacceptable toxicity is observed prior to the enrollment of 3 subjects e.g., two subjects experience DLT before the third subject enrolls. A dose level will be considered unsafe, with unacceptable toxicity and no additional subjects enrolled at that dose level and above, if it has an estimated 95% or greater probability of exceeding the target DLT rate of 30%. The maximum number of subjects evaluated for DLT for each dose level will be 12 subjects (about 4 cohorts of 3 subjects) if the dose escalation decision is to stay at the current dose from the first 3 cohorts.

Based on the above design, the dose escalation decision rules are as the following for each dose level:

- When the number of DLT evaluable subject is <12 subjects:
  - Dose escalate if the observed DLT rate <25%;

- Stay at the current dose if the observed DLT rate between 25%-33%;
- Dose de-escalate if the observed DLT rate >33%;

- After reaching the maximum 12 subjects, the dose escalation decision will be either escalate or de-escalate as follows:
  - Dose escalate if the observed DLT rate ≤25%;
  - Dose de-escalate if the observed DLT rate ≥33%;

See Table 2 for dose escalation decision rules based on the total number of subjects evaluable for DLT and the number of DLTs observed.

Table 2 Dose Escalation Decision Rules for Each Dose Level based on mTPI-2

Number of Subjects with DLTs	Number of Subjects in DLT Evaluable Population									
	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E	E	E
2	D	D	D	S	S	S	E	E	E	E
3	DU	DU	D	D	D	D	S	S	S	E
4	.	DU	DU	DU	D	D	D	D	D	D
5	.	.	DU	DU	DU	DU	DU	D	D	D
6	.	.	.	DU	DU	DU	DU	DU	DU	D
7	.	.	.	.	DU	DU	DU	DU	DU	DU
8	.	.	.	.	.	DU	DU	DU	DU	DU

E = escalate to the next higher dose level	**S = stay at the current dose level**
D = de-escalate to the next lower dose level	**DU = de-escalate to the next lower dose level and current dose level will never be used again due to unacceptable toxicity**

3.3 Sample Size

The planned total sample size for this study is approximately 18 subjects. This sample size assumes evaluation of approximately 12 subjects across 4 dose levels in dose escalation and approximately 6 subjects in the optional pharmacodynamic cohort. The goal is to enroll approximately 6 subjects at the potential RP2D, including subjects in dose escalation and the pharmacodynamic cohort.

3.4 Duration of Study Treatment

The planned treatment duration with ITI SL-172154 should be until progressive disease. Subjects with complete resolution of all injectable lesions should discontinue treatment and continue with all relevant study assessments including disease assessments.

Treatment may continue until one of the following criteria applies:

- Disease progression per RECIST v1.1 (unless eligible for treatment beyond progression).
- Death
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Participant declines further therapy with ITI of SL-172154 in the absence of disease progression
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the judgment of the investigator
- Participant non-compliance
- Pregnancy
- Termination of the study by Sponsor

3.5 Duration of Follow-up

Subjects who discontinue IP for any reason other than withdrawal of consent will be followed for AEs for 90 days after the last dose of IP. Subjects who are withdrawn from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE. Subjects who permanently discontinue IP for reasons other than progression will continue with disease assessments until progressive disease, start of another anti-cancer therapy, withdrawal of consent, death, or end of the study, whichever occurs first.

3.6 End of Study

End of Study is defined as approximately 1 year after the last subject is dosed on cycle 1, day 1 (C1D1) or the date the study is closed by the Sponsor, whichever occurs first.

3.7 Study Assessments and Procedures

The detailed study assessments and procedures are described in section 6 of the protocol.

4. ANALYSIS POPULATIONS

Population	Description
Enrolled	All subjects who have signed the main study inform consent form.
Screen Failures	All subjects who have signed the informed consent but have not received any dose of SL-172154.
All Treated	All subjects who receive at least one dose of SL-172154. Safety data will be evaluated based on this population.

Population	Description
DLT Evaluable	All subjects in the All Treated population 1) who have received at least 2 of the 3 scheduled doses of SL-172154 during cycle 1 and completed the safety follow up through DLT evaluation period; or 2) who experienced any DLT during the DLT evaluation period. The DLT evaluation period is defined as the first 21 days. The DLT evaluable population will be used to guide dose escalation and to determine the MTD or MAD.
Response Evaluable	All subjects in the All Treated population who have a baseline disease assessment and have at least one post-baseline disease assessment or had progressed or died before the first post-baseline disease assessment.

5. GENERAL ANALYSIS CONSIDERATIONS

5.1 Data Analyses during Dose Escalation

During the dose escalation, the number of subjects with DLTs will be determined after each cohort of approximately 3 subjects has been evaluated for DLT. The summary of DLTs for each dose level will be based on the number of subjects with DLTs from all subjects dosed and evaluated at the corresponding dose level who meet the definition of the DLT Evaluable Population. Select AE summary tables and listings may be provided during dose escalation to support dose escalation decisions.

5.2 Reporting Conventions

The statistical analyses will be reported using summary tables, figures, and data listings. The International Conference on Harmonization (ICH) numbering convention will be used for tables, listings, and figures.

Unless specified otherwise, all summary tables will be presented by dose level and cohort (dose escalation and pharmacodynamic) and all subjects in the analysis population. Subjects at the same dose level from dose escalation and pharmacodynamic cohorts will also be pooled together for summary tables. Select safety summary tables will be provided for the dose escalation cohorts.

Data from all participating sites will be pooled prior to data analysis. It is anticipated that subject accrual will spread thinly across sites and summaries of data by site would be unlikely to be informative and will therefore, not be provided.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in the corresponding categories. All confidence intervals (CIs) will be constructed at the 95% confidence level. Percentages are routinely based on the total number of the specified population N if not otherwise mentioned.

Individual subject data obtained from the electronic case report forms (eCRFs), central lab, and any derived data will be presented by cohort, dose level and subject in data listings. Data from all assessments, whether scheduled or unscheduled, will be included in the listings. Listings will present the data in their original format (without any imputation).

Summaries by planned time will include data from scheduled assessments and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data, when summarized, will be included only in calculation of the maximum or minimum value over time such as worst-case post-baseline. If multiple assessments are reported on the same date for the same scheduled planned time, then the worst-case result will be analyzed.

The precision of the original measurements will be maintained in summaries and listings, when possible. Generally, means, medians and standard deviations will be presented with an increasing level of precision. Means and medians will be presented to one more decimal place than the raw data, and the standard deviations will be presented to two more decimal places than the raw data.

When rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place (i.e., integers), values ≥ XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to “lost to follow-up,” this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.

All analyses and tabulations will be performed using SAS® v9.4 or above.

5.3 Data Handling

5.3.1 Premature Withdrawal and Missing Data

Subjects who prematurely withdraw from the study will be included in analyses up to the time of withdrawal, regardless of the duration of treatment and survival follow-up.

Missing data occurs when any requested data is not provided, leading to blank field on the collection instrument. These data will be indicated using a “blank” in subject data listings. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Subjects with unknown or missing best response will be assumed to be non-responders and will be included in the denominator when calculating percentages. Subjects with the designation of treatment relationship for adverse events (AEs) and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if the relationship to study treatment is missing, it will be assumed to be “Yes” for summary of drug-related AE or SAE.

For the time to event endpoints including DOR and PFS, the missing data handling method will be censoring. Censoring mechanisms for these endpoints are described in section **Error! Reference source not found.**.

The length of study treatment for each subject will depend on the safety, tolerability, and efficacy of the treatment, so the duration of treatment will vary across subjects. Subjects with shorter duration of treatment due to the natural history of their disease or medical necessities of treatment of their disease will not be considered to have missing data.

5.3.2 Baseline and Change from Baseline

Unless otherwise specified, the baseline value is defined as the last value obtained on or before the date and time of the first SL-172154 dose on Cycle 1 Day (C1D1). Post-baseline values are defined as value obtained after the first dose of SL-172154. Change from baseline is calculated as: (post-baseline value - baseline value). The percent change from baseline is calculated as: (change from baseline/baseline value) *100. If either baseline or post-baseline value is missing, the change from baseline and percent change from baseline is set to be missing as well.

5.3.3 Study Day and Duration

The reference date for age calculation is the date of consent form signed as age is an eligibility requirement. The reference date for safety, efficacy and other data analyses is the date of the first dose.

- **Study Day –** Study Day 1 is defined as the date of the first dose; the day before the first dose is defined as Study Day -1. For a given event date, Study Day is calculated relative to the date of first dose of study drug.

  Study Day = [Event Date – First Dose Date] (in days) + 1 day,
  where the event date is on or after the first dose date.

  Study Day = [Event Date – First Dose Date] (in days),
  where the event date is before the first dose date.

- **Duration (Days) –** A duration in days is calculated as the number of days between one date (Date1) and another later date (Date2)

  Duration (days) = [Date2 – Date1] (in days) + 1 day.

- **Duration (Months) –** A duration in months is calculated as the duration in days divided by 365.25/12, rounded to one decimal place.
- **Duration (Years) –** A duration in years is calculated as the duration in days divided by 365.25, rounded to one decimal place.

5.3.4 Imputation of Partial Date

In general, imputed partial dates will not be used to derive study day or duration variables. In addition, imputed partial dates are not used for the time to event endpoint analysis. However, partial dates may be imputed for exploratory analysis. The imputed partial data will be flagged in

the dataset to indicate the level of imputation. Imputed dates will not be displayed in the data listings.

6. STUDY POPULATION

Unless specified otherwise, all summary tables and data listings for the study population will be based on the All Treated Population.

6.1 Subject Disposition

Summaries of study population and subject disposition will include the number of subjects in each analysis population, the number of subjects by study status, and the primary reason for study completion/discontinuation. Study population and subject disposition information will be presented in a data listing. Both summary table and listing will be based on the Enrolled population.

Summaries of study treatment status will include the number of subjects by treatment status, and the primary reason for study treatment discontinuation. Subject treatment discontinuation information will be presented in a data listing.

6.2 Protocol Deviations

Number of subjects for each protocol deviation type and subtype will be summarized for all protocol deviation and key protocol deviations, respectively. Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan. A listing with deviation details will be provided for all protocol deviations.

6.3 Demographic

Demographic variables include age, sex, ethnicity, race, and weight and height at screening. Descriptive statistics will be presented for age, weight, and height. Frequency counts and percentages will be presented for age groups (<18 years, 18 to <65 years, 65 to <75 years and ≥75 years), sex, ethnicity, and race. All demographic data will be presented in a data listing for All Treated subjects.

6.4 Study Cancer History

General study cancer history information including the tumor type, human papilloma virus status, and time since initial diagnosis will be summarized in tables. In addition, primary anatomic site of tumor and extent of disease will be summarized for CSCC; and primary anatomic site of tumor, stage at study entry, and status of tobacco use will be summarized for SCCHN. All study cancer history data will be presented in a data listing.

6.5 General Medical and Surgical History

General medical history and surgical history along with start/end date and ongoing status at study entry will be presented in a data listing.

6.6 Prior Anti-Cancer Treatment

Prior study cancer systemic treatment drugs will be coded using the World Health Organization (WHO) Drug Dictionary. Prior study cancer systemic treatment including regimen number, drug name, start/end date, duration, intent, best response, and data of progression on the most recent regimen will be presented in a data listing. The number of prior systemic regimens for all intents, and number of prior systemic regimens for advanced/metastatic disease will be included in the summary table. Summary will be provided by dose levels/cohorts and all subjects in the analysis population.

Prior anti-cancer surgical treatment including the date and intent of procedure will be presented in a data listing. Prior anti-cancer radiotherapy including the start/end date and intent of radiotherapy will be presented in a data listing.

6.7 Study Drug Exposure

The individual subject SL-172154 ITI administration at each dosing visit will be provided in a data listing. This listing will include assigned dose level, study drug lot number, total dose injected (mg), total volume injected, injection date, start/end of injection time, injection outcome and overdose assessment along with reason. For each target, non-target and new lesion at each dosing visit, the lesion number, location, injection administration status (Yes/No), injected volume, and administration method will also be included in the data listing.

The following SL-172154 ITI administration information will be summarized:

- Number of doses received, which is the total number of dosing visits with non-zero dose injected.
- Duration of SL-172154 treatment is defined as:
    - Minimum of (data cutoff date plus 1 day or date of last dose + 21 days if last dose is C2D1 or beyond or + 7 days if last dose is C1D1, C1D8 or C1D15) minus date of first study drug administration for subjects who are on treatment.
    - Minimum of (date of death plus 1 day, data cutoff date plus 1 day, or date of last dose + 14 days if last dose is C2D1 or beyond or + 7 days if last dose is C1D1, C1D8 or C1D15) minus date of first study drug administration for subjects who discontinued from treatment.

In addition to mean, median, minimum and maximum, duration on treatment will also be summarized as <6 weeks, >=6 to <12 weeks, and >=12 weeks.

Individual duration of SL-172154 treatment will be plotted using horizontal bar graph with information on dose level, cancer type, time of responses (RECIST 1.1), best response and treatment status for each subject.

6.8 Concomitant Medications

Concomitant medications will be mapped to Anatomical Therapeutic Chemical (ATC) class and Generic Drug Names using the WHO Drug Dictionary. Concomitant medications will include medications taken on or after the date of the first dose of study drug. Any medications that are started prior to the date of the first dose but continued beyond the date of first dose will be counted as concomitant medications. Concomitant medications along with dose, route, start/end date, and indication for each medication will be presented in a data listing.

6.9 Concomitant Procedures

Concomitant procedures include cancer-related or treatment-related procedures or palliative radiotherapy that is administered while on study therapy. Concomitant procedures along with start/end date and indication for the procedure will be presented in a data listing.

7. EFFICACY ANALYSES

The efficacy endpoints include objective response, TTR, DOR, PFS, and change from baseline lesion diameter for injected lesion and non-injected lesions. All efficacy endpoints are based on the investigator disease assessment per RECIST 1.1. The efficacy analyses will be based on the All Treated population and Response Evaluable population. Unless specified otherwise, all efficacy data summaries will be presented by dose levels/cohorts, cancer type and all subjects in the analysis population.

Disease assessment will be performed at baseline (screening visit) and at the following intervals until disease progression: every 6 weeks until week 54, every 12 weeks up to year 2, and every 24 weeks until study conclusion. Confirmatory scans should be performed at least 4 weeks (>28 days) after initial documentation of an objective response and preferably at the next scheduled disease assessment that is 6 weeks later. If subjects discontinue study treatment prior to progressive disease, they should continue to be followed with radiologic disease assessments until disease progression, start of a new anti-cancer therapy, withdrawal of consent or death, whichever is earlier.

7.1 Objective Response Rate

The ORR is defined as the proportion of subjects whose best overall response is a confirmed CR or confirmed PR based on investigator assessment according to RECIST 1.1. The ORR will be estimated with a 95% CI using the exact probability method. The number and percent of subjects with the best overall response of CR, PR, SD, PD and not evaluable (NE) will be summarized. Summary of objective response will be provided for the All Treated population and Response Evaluable population.

The best overall response based on RECIST 1.1 is defined as the best overall response among all post-baseline timepoint assessments until the first PD per RECIST 1.1 or start of new anti-cancer therapy, whichever is earlier. For subjects who have not met the criteria for PD per RECIST1.1

or have not started a new anti-cancer therapy, the best overall response is defined as the best overall response among all post-baseline timepoint assessments.

Based on the investigator assessment of overall response per RECIST 1.1 at post-baseline assessments, the best overall response will be determined programmatically as the following and
Table 3:

- CR > PR > SD > PD > NE
- CR = at least two determinations of CR with at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better with at least 4 weeks apart before progression (and not qualifying for CR).
- SD = at least one SD or better ≥ 35 days after the first dose and before progression (and not qualifying for a CR or PR). The minimum interval from the first dose date for the best response of SD is 6 weeks minus 7 days to allow for visit windows of ± 7 days (35 days).
- If the minimum interval for SD is not met, the best response will depend on the subsequent assessments. See table 3 for details.
- PD is considered the best overall response when PD is documented and a best overall response of CR, PR, or SD could not be established before documentation of PD. Clinical progression will not be considered as documented disease progression in the determination of the best overall response.
- NE is considered the best overall response when PD has not been documented and a best response of CR, PR or SD could not be established.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	**Overall response Subsequent time point**	**BEST overall response**
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD, provided minimum criteria for SD duration met, otherwise, PD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

Overall response First time point	Overall response Subsequent time point	BEST overall response
NE	NE	NE

The best percent change from baseline in target lesion sum of diameters is defined as the largest reduction or smallest increase (in the case where a reduction does not occur) from baseline observed over all post-baseline disease assessments and will be presented using a waterfall plot.

Target lesion, non-target lesion, new lesion and response assessments will be presented in data listings. The percent change from baseline/nadir in target lesion sum of diameters will be kept 2 decimal places (xx.xx%) in the data listing and rounding is not required.

7.2 Time to Response

The TTR is defined as the time from the first dose until the first documentation of a subsequently confirmed objective response (confirmed CR or confirmed PR) based on RECIST 1.1. Only subjects who have achieved confirmed objective response will be evaluated for TTR. TTR will be summarized descriptively and graphically using Kaplan-Meier methods if data warrants. Individual TTR will be presented in a data listing.

7.3 Duration of Response

The DOR is defined as the time from the date of the first CR or PR (confirmed at least 28 days later) to the date of first documented disease progression per RECIST 1.1 or death, whichever occurs first. Only subjects who have achieved a confirmed CR or confirmed PR will be evaluated for DOR. If a disease progression does not occur, DOR will be censored as of the date of the last evaluable disease assessment. The evaluable disease assessment is defined as an assessment for which the overall response can be determined. DOR will be summarized descriptively and graphically using Kaplan-Meier methods if data warrants. Individual DOR will be presented in a data listing.

7.4 Progression Free Survival

The PFS is defined as time from the first day of treatment to the first documented disease progression per RECIST 1.1 or death, whichever occurs first. Subjects who have not progressed at the time of analysis will be censored at the latest date of assessment from their last evaluable disease assessment. The censoring guidance and the date of PD/death or censoring are given in the

Table 4. PFS will be summarized using Kaplan-Meier method if data warrants. Individual PFS will be listed for the All Treated population.

Table 4. Summary of Censoring Guidelines for PFS based on RECIST1.1

Situation	**Date of PD/Death or Censoring**	**PFS Outcome**
Documented PD or death	Date of the PD or death, whichever comes first	Event (unless the censoring rule specified below)
Death or PD immediately after ≥ 2 consecutive missed or non-evaluable disease assessments[1] as per the protocol specified assessment schedule	Date of last evaluable disease assessment prior to missed or non-evaluable assessments, or the first dose of investigational product, whichever occurred last	Censored
No PD or death at time of analysis or lost to follow-up	Date of last evaluable disease assessment	Censored
No baseline disease assessment OR no post-baseline disease assessment AND no death prior to second scheduled post-baseline disease assessment	Date of first dose	Censored

[1] Two or more consecutive disease assessments is defined as ≥ 16+1 weeks for the first 6 months or ≥ 24+1 weeks for 6-24 months (two disease assessments as per protocol plus a one week visit window) after the last evaluable post-baseline disease assessment. If a subject has two or more consecutive missed or non-evaluable assessments followed by an assessment showing no radiologic disease progression, then the assumption will be that the subject did not progress during the missed or non-evaluable assessments.

7.5 Change from Baseline for Injected and Non-injected Lesions

Change from baseline diameter for each individual injected and non-injected lesion will be provided in a data listing. The best percent change from baseline for each individual injected and non-injected lesion will be presented using a waterfall plot.

8. SAFETY ANALYSES

Unless specified otherwise, all safety data summaries will be presented by dose levels/cohorts and all subjects based on the All Treated population. Safety analyses will include Maximum Tolerated Dose (MTD) evaluation, AEs, laboratory test results (hematology, chemistry, coagulation), death, vital signs/pulse oximetry/weight, ECOG, cardiac evaluation (ECG), and blood phenotype (ABO/Rh) with direct antiglobulin test (DAT).

8.1 Maximum Tolerated Dose Evaluation

The Maximum Tolerated Dose (MTD) evaluation will be based on the DLT Evaluable Population. The number and percentage of subjects with DLT will be presented by dose level for dose escalation cohorts. The MTD level will be indicated in the summary.

The MTD will be estimated using isotonic regression (based on the DLTs observed in the DLT evaluable subjects). A MAD will be reported if the DLT rate never reaches ≥25%. Otherwise, an MTD will be reported. Isotonic regression is a way to estimate the MTD under the assumption that toxicity increases with dose. When using isotonic regression, the first step is to identify the doses where the dose-toxicity monotonicity assumption is violated. The DLT estimate is then adjusted for the violators such that the final estimate of the DLT rate increases with the dose. The target DLT rate is then used to select the MTD. For example, suppose that when the trial is completed, the observed DLT rates [# subjects who experienced DLT]/[# evaluable subjects] at five dose levels are (0/3, 1/3, 0/3, 4/15, 2/4). In this example the observed DLT rate at Dose Level 2 (i.e., 1/3=33%) is higher than the observed DLT rate at Dose Level 3 (i.e., 0/3=0%). To adjust for this violation, the DLT estimates are replaced with their average, i.e., (1/3+0/3)/2=1/6, resulting in the isotonic regression DLT estimates (0/3, 1/6, 1/6, 4/15, 2/4) = (0%, 16.7%, 16.7%, 26.7%, 50%), which monotonically increases with the dose level. Based on this isotonic estimate, assuming that the trial goal is to find the dose with the DLT rate of 30%, Dose Level 4 will be selected as the MTD. If there are no violators of the dose-toxicity monotonicity assumption, isotonic regression directly uses the observed DLT rates as the final estimates for MTD selection. For subjects who undergo intra-subject dose escalation, only DLTs that occur during the DLT period on the subject's initial dose level the assignment will be used for MTD determination.

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach will be used: among all tied dose levels the highest dose level with target toxicity ≤ 30% will be selected, unless all tied dose levels have estimated toxicity > 30%, in which case the lowest dose level will be selected.

8.2 Adverse Events

The AE terms on the eCRFs will be mapped to the preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Drug-related AEs are defined as AEs with relationship to study treatment being related or possibly related. A worst-case scenario approach will be taken to handle missing data, i.e., AEs with the relationship to study treatment as missing will be counted as drug-related AEs.

An overview summary of AEs will be produced, in which counts and percentages of subjects with any AE, drug-related AEs, DLT, SAEs, drug-related SAEs, fatal AEs, immune related AEs, Grade 3 or 4 AEs, and AEs leading to drug withdrawn, dose not given/held, and dose not completed.

The AE summary tables will use the following algorithms for counting subjects with AEs:

- **Preferred term rows:** each subject is counted once within each unique preferred term at the maximum grade. For example, if a subject has two headaches, the subject is counted only once under the preferred term "Headache". Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **SOC rows:** each subject is counted only once at the maximum grade at each SOC level although they may have several different preferred term events within the same SOC.
- **Any event row**: each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

All AEs and drug-related AEs will be summarized by MedDRA system organ class, preferred term and maximum toxicity grade. The non-serious AEs will be summarized by MedDRA system organ class and preferred term. The system organ class and preferred terms will be ordered by descending order of the subject incidence of system organ classes and preferred terms within each system organ class based on all subjects in the analysis population.

The following summary tables will be presented by MedDRA preferred term, in which the preferred terms will be order by descending order of subject incidence of preferred terms based on all subjects in the analysis population.

- Summary of all AEs.
- Summary of drug-related AEs.
- Summary of SAEs.

Listings of all AEs and DLTs will be presented in data listings. Listing of all AEs for the Screen Failures population will be presented in a data listing.

8.3 Clinical Laboratory Evaluation

The clinical laboratory evaluation includes the following:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential.
- Clinical chemistry: blood urea nitrogen, creatinine, glucose, sodium, potassium, calcium, magnesium, phosphorus, total protein, albumin, lactate dehydrogenase, bicarbonate, haptoglobin, ferritin, C reactive protein and liver panel (ALT, AST, total and direct bilirubin, and alkaline phosphatase).
- Coagulation: prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen, and D-dimer.

The clinical laboratory grades will be reported using the CTCAE v5.0. Separate listings will be provided for haematology, clinical chemistry, and coagulation tests. For each listing, baseline value will be specified for each subject.

Clinical laboratory results will be summarized for worst case shift from baseline toxicity grade. Frequencies of maximum observed Grade 0-4 toxicity, as defined by the NCI CTCAE v5.0, will be presented for each laboratory parameter. The determination of the maximum grade post-baseline takes into account both planned and unscheduled assessments. Separate summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate.

8.4 Death

All death records will be presented in a data listing.

8.5 Blood Phenotype and Direct Antiglobulin Test

Blood phenotype and DAT assessment date and result will be presented in a data listing.

8.6 Vital Signs and Pulse Oximetry

Vital signs (blood pressure, heart rate, respiration rate, temperature), body weight and pulse oximetry will be presented in a data listing.

8.7 Cardiac Evaluations

Cardiac evaluation in triplicate measurements will be evaluated at C1D1 and C2D1. Average value of triplicate measurements for heart rate, RR interval, uncorrected QT, QTcB and QTcF will be calculated for each timepoint on C1D1 and C2D1. Change from baseline will be calculated using average value for 1 hour and 4 hours post EOI at C1D1 and Predose at C2D1 minus C1D1 predose average value for each ECG parameter. Cardiac evaluation at screening, C1D1 and C2D1will presented in a data listing.

8.8 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status scores will be summarized for baseline, and worst-case shift from baseline in a table and presented in a data listing.

9. PHARMACOKINETIC ANALYSES

Pharmacokinetic data analyses will be based on the PK population. If PK analysis assay is performed, serum concentrations for SL-172154 will be summarized and listed, and PK parameters will be summarized and analyzed using appropriate statistical method. If ADA analysis is performed, individual subject ADA data will be summarized by dose level and presented in a data listing.

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

Pharmacodynamic and biomarker data analyses will be based on the pharmacodynamic population. If the analysis assays are performed, the pharmacodynamic and biomarker results will be summarized by dose level/visit and presented in a data listing.

11. LITERATURE REFERENCES

1. National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, NCI, NIH, DHHS, November 27, 2017.
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-47.
3. Brookmeyer, R. and Crowley, J. (1982). A confidence interval for the median survival time. Biometrics 38 29-41.
4. Guo W, Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials 2017; 58:23-33.

12.APPENDIX: LIST OF TABLES, FIGURES AND LISTINGS

12.1 List of Tables

ICH Heading	Table Number	Table Description	Analysis Population
12.1		**Demographics**	
	14.1.1	Study Populations and Subject Disposition	All Enrolled
	14.1.2	Protocol Deviations and Key Protocol Deviations	All Treated
	14.1.3	Study Treatment Status	All Treated
	14.1.4	Demographic and Baseline Characteristics	All Treated
	14.1.5	Study Cancer History	All Treated
	14.1.6	Prior Anti-Cancer Systemic Treatment	All Treated
14.2		**Efficacy**	
	14.2.1	Objective Response with Confirmation by RECIST 1.1	All Treated
	14.2.2	Objective Response with Confirmation by RECIST1.1	Response Evaluable
14.3		**Safety**	
14.3.1		**Study drug exposure/adverse event**	
	14.3.1.1	Study Drug Exposure	All Treated
	14.3.1.2	Overall Summary of Adverse Events	All Treated
	14.3.1.3	All Adverse Events by System Organ Class, Preferred Term and Maximum Toxicity Grade	All Treated
	14.3.1.4	All Adverse Events by Preferred Term	All Treated
	14.3.1.5	Serious Adverse Events by Preferred Term	All Treated
	14.3.1.6	Drug-Related Adverse Events by Preferred Term	All Treated
	14.3.1.7	Dose Limiting Toxicities	DLT Evaluable
	14.3.1.8	Non-Serious Adverse Events by System Organ Class and Preferred Term	All Treated
14.3.5		**Laboratory**	
	14.3.5.1	Hematology – Maximum CTCAE Grade Shift from Baseline	All Treated
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14.3.6		**Other Safety Data**	
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12.2 List of Figures

ICH Heading	Figure Number	Figure Description	Analysis Population
14.2	14.2.1	Plot of Duration on Treatment and Response	All Treated
	14.2.2	Plot of Maximum Reduction in Sum of Lesion Diameters for Target Lesions	All Treated
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12.3 List of Data Listings

ICH Heading	Listing Number	Listing Description	Analysis Population
16.2		**SUBJECT DATA LISTINGS**	
16.2.1		**Discontinued subjects**	
	16.2.1.1	Study Population and Subject Disposition	All Enrolled
	16.2.1.2	Study Treatment Discontinuation	All Treated
16.2.2		**Protocol deviations**	
	16.2.2.1	Protocol Deviations	All Treated
16.2.4		**Demographics**	
	16.2.4.1	Demographic and Baseline Characteristics	All Treated
	16.2.4.2	Medical and Surgical History	All Treated
	16.2.4.3	Study Cancer History	All Treated
	16.2.4.4	Prior Anti-Cancer Systemic Treatment	All Treated
	16.2.4.5	Prior Surgery and Radiotherapy Treatment	All Treated
	16.2.4.6	Concomitant Medications	All Treated
	16.2.4.7	Concomitant Procedure	All Treated
16.2.5		**Study Drug Exposure**	
	16.2.5.1	Study Drug Exposure	All Treated
16.2.6		**Individual efficacy response data**	
	16.2.6.1	Target Lesions	All Treated
	16.2.6.2	Non-Target Lesions	All Treated
	16.2.6.3	New Lesions	All Treated
	16.2.6.4	Disease Responses by RECIST 1.1	All Treated
	16.2.6.5	Time to Response and Duration of Response Based on RECIST 1.1	All Treated
	16.2.6.6	Progression-Free Survival Based on RECIST 1.1	All Treated
	16.2.6.7	Injected and Non-injected Target Lesions	All Treated
16.2.7		**Adverse Event Listings**	

ICH Heading	Listing Number	Listing Description	Analysis Population
	16.2.7.1	All Adverse Events	All Treated
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	16.2.7.3	Serious Adverse Events	All Treated
	16.2.7.4	Death	All Treated
	16.2.7.5	All Adverse Events for Screen Failure Population	Screen Failure
16.2.8		**Individual Laboratory Measurements**	
	16.2.8.1	Hematology	All Treated
	16.2.8.2	Clinical Chemistry (including ferritin and haptoglobin)	All Treated
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16.2.9		**Listing of other safety data**	
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	16.2.9.2	ECOG Performance Status	All Treated
	16.2.9.3	Cardiac Assessments (ECG)	All Treated
	16.2.9.4	Blood Phenotyping and Direct Antiglobulin Test	All Treated