Statistical Analysis Plan

Title: Statistical Analysis Plan for Protocol SL01-DEL-101: Phase 1 Dose Escalation and Dose Expansion Study of an Agonist Redirected Checkpoint Fusion Protein, SL-279252 (PD1-Fc-OX40L), in Subjects with Advanced Solid Tumors or Lymphomas

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LIST OF ABBREVIATIONS

ADA	Anti-drug-antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the serum concentration time curve
CI	Confidence interval
CBR	Clinical Benefit Rate
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C*x*D*y*	Cycle *x* Day *y*
DL	Dose level
DLT	Dose limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ICH	International Conference on Harmonisation
iCPD	Immune confirmed progression of disease
iCR	Immune complete response
iPR	Immune partial response
iRECIST	Immune response evaluation criteria in solid tumors
irAE	Immune related adverse event
IRR	Infusion-related reaction
irSAE	Immune-related serious adverse event
iSD	Immune stable disease
iUPD	Immune unconfirmed progression of disease
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor Response
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response

PT	Preferred term
RECIL	Response evaluation criteria in lymphoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented during the analyses of data collected within the scope of Protocol Number SL01-DEL-101, Phase 1 Dose Escalation and Dose Expansion Study of an Agonist Redirected Checkpoint Fusion Protein, SL-279252 (PD1-Fc-OX40L), in Subjects with Advanced Solid Tumors or Lymphomas:

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Final Version v0.0	05November2018
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Amendment Version v02	18June2019
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The purpose of this analysis plan is to provide specific guidelines from which the analysis of this study will proceed. Separate analysis plans will be provided for the pharmacokinetic (PK)/pharmacodynamic (PD) data. 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 (CSR).

2. STUDY OBJECTIVES AND OUTCOME MEASURE

Objective	Outcome Measure
Primary Objectives	
Dose Escalation: To evaluate the safety and tolerability and to identify the maximum-tolerated dose (MTD) or maximum administered dose (MAD) of SL-279252 in subjects with select locally advanced or metastatic malignancies (i.e., solid tumors or lymphomas) **Dose Expansion:** To further refine the safety and tolerability of SL-279252 in subjects with select locally advanced or metastatic select malignancies (i.e., solid tumors or lymphomas)	Safety/tolerability outcomes include: Incidence of all adverse events (AEs) and immune-related adverse events (irAEs), serious adverse events (SAEs), fatal SAEs, dose limiting toxicity (DLT), AE and irAEs leading to discontinuation; changes in safety assessments (e.g., laboratory parameters, vital signs, etc.) per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE – version [v]) 5.0). **Dose Escalation**: The MTD is defined based on the rate of DLTs and the MAD is the highest dose administered. **Dose Expansion**: Infusion-related reactions (IRRs) and discontinuation of SL-279252 will be closely monitored using sequential boundaries.
Secondary Objectives	

Dose Escalation and Dose Expansion: To select the dose and schedule i.e., recommended Phase 2 dose (RP2D) for SL-279252	Based on review of data collected during dose escalation and expansion, including safety, tolerability, pharmacokinetics (PK), anti-tumor activity outcomes, pharmacodynamic outcomes.
Dose Escalation and Dose Expansion: To assess preliminary evidence of anti-tumor activity of SL-279252	Response assessment according to immune response evaluation criteria in solid tumors (iRECIST) for solid tumors or response evaluation criteria in lymphoma (RECIL) 2017 for lymphomas • Objective response rate (ORR; proportion of participants whose best overall response is a complete response [CR] or partial response [PR] evaluated via iRECIST, therefore referred to as iCR or iPR) • Clinical benefit rate (CBR; proportion of participants whose best overall response is an iCR, iPR or stable disease (iSD) of ≥16 weeks);
Secondary Objectives	
Dose Escalation and Dose Expansion: To evaluate immunogenicity to SL-279252 during and after treatment	• Number and proportion of participants with positive anti-drug-antibody (ADA) titer • ADA duration • Transient vs. Persistent ADA
Dose Escalation and Dose Expansion Cohorts: To characterize the PK of SL-279252	• 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-279252 • Area under the serum concentration-time curve (AUC) • Terminal elimination half-life ($t_{½}$), Clearance (CL) and Volume of Distribution (Vz)
Exploratory Objectives	
Dose Escalation and Dose Expansion: To assess target engage-ment of PD-L1 and OX40 on peripheral blood mononuclear cells (PBMCs) prior to, on-treatment, and following SL-279252 administration.	Free/total receptor occupancy of OX40 and PD-L1 in circulating CD45 positive cells by flow cytometry with further sub-gating into B and T cell subsets.

Dose Escalation and Dose Expansion Cohorts: To assess biomarkers in blood prior to, on-treatment, and following SL-279252 administration.	Pharmacodynamic biomarkers in blood: • Changes from baseline in plasma cytokine levels • Changes from baseline in cell counts and percentages of circulating immune cells • Complement activation by assessment of SC5b-9 terminal fragment Baseline biomarker: • Cell-free tumor nucleic acid (cfNA) for tumor mutational burden (TMB) analysis [Dose Expansion ONLY]
Dose Escalation and Dose Expansion: To assess tumor biomarkers prior to, on-treatment, and following SL-279252 administration.	Describe changes observed in the tumor microenvironment (TME) in pre- and post-treatment tumor biopsies

3. STUDY DESIGN AND PLAN

This trial is a Phase 1 first in human, open label, dose escalation and dose expansion study to evaluate the safety, tolerability, PK, anti-tumor activity and pharmacodynamic effects of SL-279252 in subjects with selected locally advanced or metastatic malignancies.

3.1 Study Design

The study design consists of Dose Escalation and Dose Expansion cohorts. The screening period will be 21 days prior to the first dose in the dose-escalation cohorts. Dosing will occur in cycles of 28 days until one of the following criteria applies: disease progression per iRECIST or RECIL 2017, death, intercurrent illness that prevents further administration of treatment, unacceptable AE(s), participant decides to withdraw from the study, general or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator, participant non-compliance, pregnancy, termination of the study by Sponsor. Response and disease progression will be assessed at predetermined intervals.

Subjects with any of the following malignancies (including specific subtypes) may be enrolled in Dose Escalation: melanoma, NSCLC (squamous cell or adenocarcinoma or adeno-squamous), urothelial cancer, HNSCC, squamous cell cervical cancer, gastric or GEJ adenocarcinoma, SCCA, Skin-SCC, RCC, HL, MSI-H or MMRD solid tumors excluding CNS malignancies. The tumor types for dose expansion will be determined after review of data collected during dose escalation and will be selected from the dose escalation list of malignancies.

In the dose escalation phase of the study, subjects will be enrolled into sequential dose levels (DL) as outlined in Section 3.2 and Table 2. Enrollment into a DL cohort will follow the Keyboard Design with a target DLT rate of 30% (and the acceptable range is 25-33.3%), as in Table 1.

Two possible schedules (Schedule 1 and Schedule 2) may be explored. Schedule 1 will be evaluated first. A transition to Schedule 2 may be implemented for reasons outlined in Protocol Section 3.2.7. If Schedule 2 is opened, the Sponsor may also elect to stop enrollment in Schedule 2 early (e.g., based on safety) and resume enrollment in Schedule 1. The MTD or MAD may be determined for either schedule 1 or Schedule 2. Alternatively, a less intensive dosing schedule may be instituted if safety and pharmacodynamic data on Schedule 1 supports less frequent dosing of SL-279252.

Table 1. Keyboard Design Decision Rules

Action	Number of evaluable subjects treated at the current dose level											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2	2	2	2
Stay at same dose if # of DLT =	NA	NA	1	1	NA	2	2	2	3	3	3	3 or 4
De-escalate if # of DLT ≥	1	1	2	2	2	3	3	3	4	4	4	5
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5	6	6	7

Notes:

a. "Eliminate" means that the current and higher doses are eliminated from the trial to prevent treating any future subjects at these doses because they are overly toxic. When a dose is eliminated, automatically de-escalate the dose to the next lower level. If the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.

b. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat new subjects at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.

c. If the current dose is the highest dose and the rule indicates dose escalation, treat new subjects at the highest dose.

Based on accumulating data from the dose escalation phase, up to 2 Dose Expansion cohorts may be opened. Only one schedule will be evaluated in the expansion phase. Continuous toxicity monitoring (using sequential boundaries) will be used within each cohort. Accrual will be temporarily stopped if excessive numbers of subjects with ≥ Grade 3 infusion related reactions (IRRs) are observed (i.e., if *bn* out of *n* subjects experience ≥ Grade 3 IRRs as described in the table below). This is a Pocock-type stopping boundary that yields a probability of crossing the boundary of 0.05 at most when the rate of ≥ Grade 3 IRRs is equal to the acceptable rate of 30%.

Number of subjects, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary, *bn*	-	-	-	4	5	5	6	6	6	7	7	8	8	9	9

Similarly, accrual will be temporarily stopped if excessive discontinuations due to toxicity are observed (i.e., if *bn* out of *n* subjects discontinue SL-279252 due to toxicity as described in the table below). This is a Pocock-type stopping boundary that yields a probability of crossing the boundary of 0.05 at most when the rate of discontinuation due to toxicity is equal to the acceptable rate of 15%.

Number of subjects, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Boundary, *bn*	-	-	3	3	4	4	4	4	5	5	5	6	6	6	6

3.2 Dose Escalation

Two or more dosing schedules for SL-279252 may be evaluated:

- **Schedule 1:** administering SL-279252 on days 1, 8 and 15 of the first 28-day cycle and then every 2 weeks thereafter on days 1 and 15 of each 28- day cycle beginning with cycle 2.
- **Schedule 2:** weekly dosing of SL-279252 on days 1, 8, 15 and 22 of each 28-day cycle.

A less frequent dosing schedule (e.g., once every three weeks or once every four weeks) may be investigated if safety data from Schedule 1 indicates that this approach is most prudent.

Table 2. SL-279252 Dose Escalation Plan

Dose Level	Dose of SL-279252 (mg/kg)[a,b,c,d,e]	Duration of Infusion[e]
Level 1	0.0001 mg/kg	5-30 minutes
Level 2	0.001 mg/kg	5-30 minutes
Level 3	0.003 mg/kg	5-30 minutes
Level 4	0.01 mg/kg	30 minutes (+/- 10 minutes)
Level 5	0.03 mg/kg	30 minutes (+/- 10 minutes)
Level 6	0.1 mg/kg	30 minutes (+/- 10 minutes)
Level 7	0.3 mg/kg	30 minutes (+/- 10 minutes)
Level 8	1.0 mg/kg	1 hour (+/- 15 minutes)
Level 9	3.0 mg/kg	1 hour (+/- 15 minutes)
Level 10	6.0 mg/kg	1 hour (+/- 15 minutes)

a) Dose escalation begins on Schedule 1: SL-279252 may be administered in the first cycle on days 1, 8, and 15 of the first 28-day cycle and then once every 2 weeks on days 1 and 15 of each 28-day cycle beginning at cycle 2.
b) Dose escalation on Schedule 2 may be tested: If Schedule 2 is opened, SL-279252 may be administered once weekly on days 1, 8, 15, and 22 of each 28-day cycle. The starting dose on schedule 2 will be at least one dose level below the current Schedule 1 dose level defined by the Keyboard design. If Schedule 2 is opened for enrollment, then enrollment on Schedule 1 will be halted.
c) Intermediate dose levels may be tested based on emerging safety data. The option to explore more than 10 dose levels on Schedule 1 or additional dose levels on Schedule 2 is also a possibility if safety allows. Escalations will not exceed half-log increments after dose level 2.
d) The actual body weight in kg will be used for dose calculation in all subjects whose body weight is ≤100 kg. For subjects with body weight >100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg.
e) Infusion time may change based on final drug volume needed for administration, safety and tolerability of the infusion for the subject, and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.

Evaluation of Schedule 1: Initially, cohort size in Schedule 1 may be limited to 1 subject for enrollment until one of the following occurs: a ≥ Grade 2 toxicity or DLT is observed (see Section 3.2.6 of protocol for DLT definitions) or DL 6 is reached; any of these scenarios will trigger

enrollment of ≥ 3 subjects in the current dose and dose level cohorts from that point forward. Multiple-subject cohorts will incorporate a minimum 3-day stagger between dosing the first and second subject at the same dose level, although this requirement may change based on emerging safety data as determined by the Safety Monitoring Committee (SMC). The incidence of DLT will be assessed over a period of 21 days during the first cycle of therapy on Schedule 1.

Evaluation of Schedule 2: If Schedule 1 is safe and tolerable, and pharmacodynamic effects are not present or detectable, this may suggest that a more frequent dosing schedule is warranted. In this event cohort enrollment on Schedule 2 will be instituted in lieu of Schedule 1.

The starting dose on Schedule 2 will be at least 1 DL lower than the current safe Schedule 1 DL defined by the Keyboard design. Dose escalation (or de-escalation) may then proceed based on a DL previously evaluated on Schedule 1 as shown in Table 1. For example, if 0.1 mg/kg (DL 6) is the current DL being evaluated on Schedule 1, then the starting dose on Schedule 2 will be 0.03 mg/kg (DL 5) or lower. A minimum of 3 subjects will be evaluated in each DL during dose escalation on Schedule 2. A minimum 3-day stagger between dosing the first and second subject at the same DL is required. The incidence of DLT will be assessed over a period of 28 days during the first cycle of therapy for Schedule 2.

Evaluation of a Less Frequent Dosing Schedule: If safety and pharmacodynamic data from Schedule 1 support exploration of a less intensive dosing schedule, then cohort enrollment on this as yet to be identified schedule will be instituted in lieu of Schedule 1.

After dosing has been completed at each dose level, safety, PK and PD data (as applicable) will be reviewed, and dose escalation decisions will be made by the SMC (composed of the Sponsor Representatives and the Principal Investigators). Dose escalation decisions will also take into consideration safety information beyond the DLT period from prior dose levels. In addition, if the SMC determines that, in the absence of DLTs, enrollment of additional subjects is required in order to better determine PK or safety, enrollment of an additional 3 subjects may be undertaken at 1 or more of the dose levels already studied. Should more than 3 subjects be accrued to a dose level for reasons other than DLT/toxicity, the decision to escalate further may be made after the first 3 subjects clear the DLT window period.

Pharmacodynamic Cohorts: The Sponsor, in consultation with the SMC, may elect to open a pharmacodynamic cohort in order to obtain additional pharmacodynamic data from a total of approximately 6 additional subjects at one or more dose levels that have previously completed evaluation for safety and has not exceeded the MTD. Subjects enrolled in the pharmacodynamic cohort will not inform dose escalation decisions but the pharmacodynamic information gathered from these additional subjects may inform selection of doses for further evaluation in dose expansion.

3.3 Dose Expansion

Based on accumulating data from the dose escalation phase, including safety, PK, pharmacodynamic and anti-tumor activity, up to two Dose Expansion Cohorts may be opened for enrollment. The expansion cohorts could potentially begin enrollment prior to the end of dose escalation. A minimum of 6 subjects must be evaluated at the dose level to be expanded to confirm

safety and tolerability prior to expansion. One or two doses of SL-279252 (on the same schedule, i.e., only one schedule will be evaluated in the expansion phase) may be expanded.

3.4 Study Assessments and Procedures

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

4. SAMPLE SIZE

If only Schedule 1 is evaluated, the maximum planned sample size is 42 for dose escalation. If Schedule 1 and 2 are both fully evaluated in dose escalation, the maximum planned sample size is 57. If pharmacodynamic cohorts are opened in dose escalation, the maximum sample size is 48 if schedule 1 is fully evaluated or 63 if Schedule 1 and 2 are fully evaluated. The sample size in each Expansion Cohort is ~15 subjects. Overall, the total sample size estimate for this study is ~ 78 subjects assuming only Schedule 1 is evaluated and pharmacodynamic cohorts are opened and ~93 subjects if both Schedule 1 and 2 are fully evaluated and pharmacodynamic cohorts are opened.

5. GENERAL ANALYSIS CONSIDERATIONS

5.1 Reporting Conventions

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

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

Unless specified otherwise, all summary tables will be presented by dose schedule/level for all subjects in the analysis population. Subjects from dose escalation and pharmacodynamic cohorts will be pooled. Summaries will be provided for each expansion cohort separately if data warrants.

All individual subject data listings will be presented by dose level, dose schedule and subject, unless specified otherwise. 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), unless specified otherwise.

Summaries by planned time point will include data from scheduled assessments and all data will be reported according to the nominal visit for which it will be 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, the worst-case result will be analyzed.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. The precision of the original measurements will be maintained in summaries and listings, when possible. Generally, 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.

Categorical variables will be summarized by counts and by percentages of subjects in the corresponding categories. Percentages are routinely based on the total number of the specified population N if not otherwise specified. For frequency counts, 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 confidence intervals (CIs) will be constructed at the 95% confidence level, unless specified otherwise.

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

5.2 Data Handling

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data.

5.2.1 Missing Data

Missing data occurs when any requested data is not provided, leading to blank field on the collection instrument. Answers such as "Not applicable", "Not evaluable", etc. are not considered to be missing data and should be displayed as such.

For the time to event endpoints including duration of response (DOR), progression free survival (PFS), and overall survival (OS), the missing data handling method will be censoring. Censoring mechanisms for these endpoints are described in Section 8.

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. Similarly, the duration of follow up for survival will also vary. All time to event endpoints will be analyzed using suitable statistical methods.

In the event that the study is prematurely discontinued, the study team will review the data to assess which statistical analyses are still considered appropriate.

5.2.2 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-279252 dose on Cycle 1 Day (C1D1). Post-baseline values are defined as value obtained after the first dose of SL-279252.

Change from baseline is calculated as:

- Post-baseline value - baseline value

The percent change from baseline is calculated as:

- (Post-baseline value - baseline value)*100/baseline value

If either baseline or post-baseline value is missing, the change from baseline and percent change from baseline will be missing.

5.2.3 Study Day, Duration, and Time from Event

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. There is no study day 0. For a given event date, Study Day is calculated relative to the date of the 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 is calculated as the stop date minus the start date plus one.

  Duration (days) = [Stop Date – Start Date] (in days) + 1 day.

- **Time since an event -**Time since an event (e.g. time since initial diagnosis) is calculated as the reference date minus the event date. For time since initial diagnosis, the reference date is the first dose of study treatment.
- **Time to an event -** Time to an event (e.g. time to response, PFS, OS) is calculated as the event date minus the reference date+1. For time to response, PFS and OS, the first dose of study treatment is the reference date.

To convert days to months, divide the number of days by 30.4375 (365.25/12) and round to one decimal place.

5.2.4 Imputation of Partial Date

In general, imputed partial dates will not be used to derive study day or duration variables, unless otherwise specified. No partial dates imputation will be performed for time to event endpoint analysis. Any imputed partial data will be flagged in the analysis datasets to indicate the level of imputation. Imputed dates will not be displayed in the data listings.

6. ANALYSIS POPULATIONS

For the analysis, the following populations are defined:

Table 3. Analysis Populations

Population	Description
Screened	All subjects who sign the main study informed consent form.
Screen Failures	A subject who signs the informed consent but has not received any dose of SL-279252.
All Treated	All subjects who receive at least one dose of SL-279252. Safety data will be evaluated based on this population.
DLT Evaluable	All subjects in the dose escalation cohorts and All Treated Population who receive at least 2 doses of SL-279252 for Schedule 1 and at least 3 doses for Schedule 2 during the DLT evaluation period, complete the safety follow up through DLT evaluation period or experience any DLT during the DLT evaluation period. The DLT evaluation period is defined as the first 21 days or 28 days of treatment on Schedule 1 or Schedule 2, respectively.
Efficacy Evaluable	All subjects in the All Treated Population who received at least 3 doses of SL-279252 and had at least one disease assessment or had progressed or died before the first post-baseline disease assessment.
Immunogenicity Population	All subjects in the All Treated Population who had at least one evaluable immunogenicity assessment.

7. STUDY POPULATION

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

7.1 Subject Disposition

Summaries of subject disposition information will include the number of subjects in each analysis population, and the primary reason for end of study participation and treatment discontinuation. Subject disposition information will be presented in a data listing.

7.2 Protocol Deviations

Incidence of major protocol deviations, minor protocol deviations, and all deviations will be summarized by deviation categories. A listing will be provided with all protocol deviations . None of the deviations will lead to subjects being excluded from any analysis populations. Other select

categories of protocol deviations including but not limited to COVID-19 related deviations may be listed or summarized.

7.3 Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, and race. Other baseline characteristics include weight and height.

Descriptive statistics will be presented for age, weight, and height. Frequency counts and percentages will be presented for age groups 18-<65 years, 65-<75 years and ≥75 years), gender, ethnicity and race. All demographic and baseline characteristics will be presented in a data listing.

7.4 Study Cancer History and Prior Cancer Therapy

Study cancer history and prior cancer therapy will be summarized in tables and presented in data listings. For the calculation of time from initial diagnosis and time since progression on most recent regimen, if there are partial dates of initial diagnosis or partial dates of progression on most recent regimen, the missing day will be imputed as "01" and the missing month will be imputed as "January".

7.5 General Medical History

General medical history will be presented in a data listing.

7.6 Study Drug Exposure

SL-279252 average dose received, number of doses received, duration of treatment, and dose compliance will be summarized.

Subject average dose is calculated as the cumulative dose (mg) that a subject received divided by the total number of doses received.

Duration of SL-279252 treatment will be summarized in weeks by continuous descriptive statistics and in the following categories: <= 4 weeks, > 4 - 8 weeks, > 8 - 16 weeks, > 16 - 24 weeks, > 24 - 48 weeks, > 48 weeks. The duration of treatment is defined as:

- Minimum of (date of death plus 1 day, data cutoff date plus 1 day, and date of last dose + 14 days for bi-weekly dosing schedule or + 7 days for weekly dosing schedule) – date of first study drug administration Dose compliance is defined as the total mg of SL-279252 taken divided by the total mg of SL-279252 assigned based on study schedule, expressed as a percentage.

7.7 Prior and Concomitant Medications

Verbatim terms on electronic case report forms (eCRFs) will be mapped to Anatomical Therapeutic Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHO) Drug Dictionary Global B3 format, September 1, 2018 release.

Prior medications are defined as medications that end prior to the date of the first dose of study treatment. Concomitant medications are defined as medications taken on or after the date of the first dose of study drug. Any medications that started prior to the date of the first dose but continued beyond the date of first dose will be counted as concomitant medications.

If both the start and end dates are completely missing, the medication will be considered concomitant. For cases where start or end dates are partially recorded, the following imputation algorithms will be used for the purpose of determining prior or concomitant medications:

- Missing start day, but month and year present:

If year and month are same as first dosing year and month, assign the day of first dosing date to the partial date. Otherwise, assign 1st of the month to the partial date.

- Missing start day and month, but year present:

If year is same as first dosing year, assign the month and day of first dosing date to the partial date. Otherwise, assign January 1st to the partial date.

- Missing end day, but month and year present:

If year and month are same as end of study participation year and month, assign the day of end of study participation to the partial date. Otherwise, assign the last day of the month to the partial date.

- Missing end day and month, but year present:

If year is same as end of study participation year, assign the month and day of end of study participation date to the partial date. Otherwise, assign December 31st to the partial date.

If the study is ongoing (e.g. interim analysis) and the study end date is not available, the cut-off date will be used instead.

Prior and concomitant medications along with dose, route, start/end date, and indication for each medication will be presented in a data listing.

7.8 Concomitant Procedures

Concomitant procedures along with the procedure dates and indications will be presented in a data listing.

8. EFFICACY ANALYSES

The efficacy analysis will be based on the All Treated population and/or Efficacy Evaluable population, as appropriate. The efficacy endpoints include ORR, CBR, time to response (TTR), DOR, tumor size change from baseline for target lesions, PFS, and OS.

Response assessment will be based on the iRECIST for solid tumors and RECIL 2017 for lymphoma. Radiographic disease assessment must be performed at screening, and at the following intervals until a disease progression is confirmed: every 8 weeks through week 24, every 12 weeks

up to year 2 and then every 6 months up to conclusion of the study. Disease assessment window is +/- 1 week. Confirmatory assessments should be performed at least 4 weeks (≥ 28 days) after the initial documentation of an objective response or an unconfirmed disease progression. Subjects who discontinue study treatment for reasons other than disease progression will be monitored for radiologic response until start of new anti-cancer therapy, disease progression, withdrawal of consent or death.

8.1 ORR Based on iRECIST for Solid Tumors

8.1.1 Time Point Tumor Response based on iRECIST

The iRECIST guidelines are based on principles used in RECIST 1.1. The response assigned using iRECIST have a prefix of "i" for assigned responses (e.g., "immune" complete response [iCR]) to differentiate them from responses assigned using RECIST 1.1). The overall responses at each assessment per iRECIST is as the following:

- Complete Response (iCR)
- Partial Response (iPR)
- Stable Disease (iSD)
- Unconfirmed Progressive Disease (iUPD) and Confirmed Progressive Disease (iCPD)
- Not evaluable (NE) = NE

8.1.2 Analysis of ORR based on iRECIST

The ORR based on iRECIST is defined as the proportion of subjects whose best overall response is a confirmed iCR or confirmed iPR. The analysis of ORR per iRECIST will be conducted by schedule/dose level for all solid tumors and selected tumor types as appropriate in the All Treated population and Efficacy Evaluable population. 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 iCR, iPR, iSD, iUPD, iCPD and NE will be summarized. The overall response at each visit along the best overall response based on iRECIST will be presented in a data listing.

8.1.3 Derivation of Best Overall Response based on iRECIST

The best overall response based on iRECIST is defined as the best overall response among all post-baseline timepoint assessments until the first iCPD or the last assessment if an iCPD has not been observed. Based on the investigator assessment of overall response at all post-baseline assessments, the best overall response will be determined according to the following:

- iCR > iPR > iSD > iCPD (iUPD if no iCPD) > NE
- iCR = iCR must be confirmed at least 4 weeks later.
- iPR = iPR must be confirmed at least 4 weeks later.
- iSD = at least one iSD or better ≥ 49 days after the first dose date and not qualifying for an iCR or iPR. The minimum interval from the first dose date for the best response of iSD is 8 weeks minus 7 days to allow for the visit windows of ± 7 days (49 days).

- iCPD = iUPD must be confirmed by a subsequent assessment at least 4 weeks later to have iCPD.
- iUPD = iUPD is not confirmed by a subsequent assessment at least 4 weeks later and not qualifying for iSD or better.
- Clinical deterioration will not be considered as documented disease progression.

8.2 ORR Based on RECIST 1.1 for Solid Tumors

8.2.1 Time Point Tumor Response based on RECIST 1.1

The overall responses at each time point assessment per RECIST 1.1 is derived from the overall response per iRECIST as the following:

- Complete Response (CR) = iCR
- Partial Response (PR) = iPR
- Stable Disease (SD) = iSD
- Progressive Disease (PD) = iUPD or iCPD
- Not evaluable (NE) = NE

8.2.2 Analysis of ORR based on RECIST 1.1

The ORR based on RECIST 1.1 is defined as the proportion of subjects whose best overall response before the first PD is a confirmed CR or confirmed PR. The analysis of ORR per RECIST 1.1 will be conducted by schedule/dose level for all solid tumors and selected tumor type as appropriate in the All Treated population and Efficacy Evaluable population. 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 NE will be summarized. The best overall response based on RECIST 1.1 will be presented in a data listing.

8.2.3 Derivation of Best Overall Response based on RECIST 1.1

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 (the first iUPD per iRECIST) or the last assessment if PD has not been observed. Based on the investigator assessment of overall response at all post-baseline assessments, the best overall response will be determined according to the following:

- CR > PR > SD > PD > NE
- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for CR).
- SD = at least one SD or better ≥ 49 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 8 weeks minus 7 days to allow for visit windows of ± 7 days (49 days).

- Clinical deterioration will not be considered as documented disease progression.

Table 4. 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
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease,
NE = not evaluable.
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

8.3 ORR Based on RECIL 2017 for Lymphomas

8.3.1 Response assessment based on RECIL 2017

The response assessment at each assessment per RECIL 2017 is as the following:

- Complete Response (CR)
- Partial Response (PR)
- Minor Response (MR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Not evaluable (NE)

8.3.2 Analysis of ORR based on RECIL 2017

The ORR based on RECIL 2017 is defined as the proportion of subjects whose best overall response is a CR or PR. The analysis of ORR per RECIL 2017 will be conducted in the All Treated population and Efficacy Evaluable population if data warrants. 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, MR, SD, PD and NE will be summarized. The overall response at each visit along with the best overall response based on RECIL 2017 will be presented in a data listing.

8.3.3 Derivation of Best Overall Response based on RECIL 2017

The best overall response is defined as the best overall response among all post-baseline timepoint assessments until the first PD or the last assessment if PD has not been observed. Based on investigator assessment of overall response at all post-baseline assessments, the best overall response will be determined as the following:

- CR > PR > MR > SD > PD > NE
- CR = at least one CR
- PR = at least one PR or better (and not qualifying for CR).
- SD = at least one SD assessment (or better) ≥ 49 days after the first dose (and not qualifying for a CR or PR). The minimum interval from the first dose date for the best response of SD is 8 weeks – 7 days to allow for visit windows of ± 7 days (49 days).
- Clinical deterioration will not be considered as documented disease progression.

8.4 Clinical Benefit Rate

The CBR based on iRECIST is defined as the proportion of subjects whose best overall response is a confirmed iCR, confirmed iPR or iSD of ≥ 16 weeks, where iSD ≥ 16 weeks is defined as at least one iSD or better for ≥ 15 weeks (16 weeks with 1 week visit window) and not qualifying for a confirmed iCR or iPR as the following:

Response at week 8 assessment	Response at week 16 assessment	Response at week 24 assessment	iSD ≥ 16 weeks
iSD	iSD/iPR/iCR	Any	Yes
iSD	iUPD	iSD/iPR/iCR	Yes
iSD	iUPD	iUPD/iCPD/NE/missing	No
iSD	NE/missing	iSD/iPR/iCR	Yes
iSD	NE/missing	iUPD/NE/missing	No
iCR/iPR/iSD/iUPD/NE	iSD	Any	Yes

The CBR based on RECIST 1.1 is defined as the proportion of subjects whose best overall response is a confirmed CR, confirmed PR or SD of ≥ 16 weeks until the first PD, where SD ≥ 16 weeks is defined as at least one SD or better for ≥ 15 weeks (16 weeks with 1 week visit window) before the first PD and not qualifying for a confirmed CR or PR as the following:

Response at week 8 assessment	Response at week 16 assessment	Response at week 24 assessment	SD ≥ 16 weeks
SD	SD/PR/CR	Any	Yes

SD	PD	Any	No
SD	NE/missing	SD/PR/CR	Yes
SD	NE/missing	PD/NE/missing	No
CR/PR/SD/NE	SD	Any	Yes

The analysis of CBR will be conducted by schedule/dose level for all solid tumors and selected tumor types as appropriate in the All Treated population and Efficacy Evaluable population. The CBR will be estimated with a 95% CI using the exact probability method.

8.5 Time to Response

TTR based on iRECIST is defined as the time from the first dose until the first documentation of a subsequently confirmed objective response (confirmed iCR or confirmed iPR). Only subjects who have achieved objective response will be evaluated for TTR.

TTR based on RECIST is defined as the time from the first dose until the first documentation of a subsequently confirmed objective response (confirmed CR or confirmed PR). Only subjects who have achieved objective response will be evaluated for TTR.

TTR based on RECIL 2017 is defined as the time from the first dose until the first documentation of an objective response (CR or PR). Only subjects who have achieved objective response will be evaluated for TTR.

If data warrants, the median and quartiles of TTR and their 95% CIs will be assessed using the Kaplan-Meier method and Brookmeyer and Crowley (1982) method, respectively, and TTR will be presented in a data listing.

8.6 Duration to Response

DOR based on iRECIST is defined as time from the date of initial response (iCR or iPR confirmed at least 28 days later) to the date of first documented disease progression that is confirmed or death, whichever occurs first. Only subjects who have achieved objective response (confirmed iCR or confirmed iPR) will be evaluated for DOR. The censoring guidance and the date of PD/death or censoring are same as that for PFS in Section 8.9.1.

DOR based on RECIST 1.1 is defined as time from the date of the first CR or PR (confirmed at least 28 days later) to the date of first documented disease progression (confirmed or not) or death, whichever occurs first. Only subjects who have achieved objective response (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 their last evaluable disease assessment. The censoring guidance and the date of PD/death or censoring are same as that for PFS in Section 8.9.2.

DOR based on RECIL 2017 is defined as time from the date of the first CR or PR to the date of first documented disease progression (confirmed or not) or death, whichever occurs first. Only

subjects who have achieved objective response (CR or PR) will be evaluated for DOR. If a disease progression does not occur, DOR will be censored as of the date of their last evaluable disease assessment. The censoring guidance and the date of PD/death or censoring are same as that for PFS in Section 8.9.3.

If data warrants, the median and quartiles of DOR and their 95% CIs will be assessed using the Kaplan-Meier method and Brookmeyer and Crowley (1982) method, respectively, and the DOR will be presented in a data listing.

8.7 Change from Baseline in Tumor Size

For response assessment based on iRECIST for solid tumors, the percent change from baseline in target lesion sum of diameters will be presented by subject using spider plots. The percent change from baseline will only be calculated when all target lesions at baseline are also present and measurable at a post baseline visit. 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 up to and including the first PD. The best percent change from baseline will be presented using a waterfall plot.

For response assessment based on RECIL 2017 for lymphoma, the percent change from baseline in target lesion sum of diameters will be presented by subject using spider plots if data warrants. The best percent change from baseline in target lesion sum of longest 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 up to and including the first PD. The best percent change from baseline will be presented using a waterfall plot if data warrants.

8.8 Other Response Data Analysis

Tumor assessment at baseline, including sum of target lesion diameters, number of subjects with target lesions and non-target lesions will be summarized in the All Treated Population for solid tumors and lymphoma, respectively, if data warrants.

For solid tumors response assessment based on iRECIST, lesion assessment including target lesion measurements and sum of diameters, non-target lesions and new lesions will be presented in data listings.

For lymphoma response assessment based on RECIL 2017, lesion assessment including target lesion measurements and sum of diameters, non-target lesions and new lesions will be presented in data listings.

8.9 Progression Free Survival

The PFS data analysis will be based on iRECIST and RECIST 1.1 for solid tumors and RECIL 2017 for lymphoma using All Treated Population.

8.9.1 PFS based on iRECIST for Solid Tumors

PFS based on iRECIST is defined as time from the first day of treatment to the first documented disease progression (iUPD) that is subsequently confirmed or death, whichever occurs first. If iUPD occurs but is disregarded because of later iSD, iPR or iCR, that iUPD date should not be used as the progression event for PFS. If iUPD is not confirmed and there is no subsequent iSD, iPR or iCR, then the iUPD date should still be used as progression event for PFS in the following scenarios: if the subjects stop study treatment because they were not judged to be clinically stable, or no further response assessments are done; the next timepoint responses are all iUPD, and iCPD never occurs; or the subject dies from their cancer.

Subjects who have not progressed at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable iRECIST assessment. The censoring guidance and the date of PD/death or censoring are given in the Table 5 below.

Table 5. Summary of Censoring Guidelines for PFS based on iRECIST

Situation	Date of PD/Death or Censoring	PFS Outcome
Documented iCPD or death	Date of the initial iUPD that is confirmed or death, whichever comes first	Event (unless the censoring rule specified below)
iUPD and if iUPD is not confirmed and there is no subsequent iSD, iPR or iCR[1]	Date of the last iUPD	Event (unless the censoring rule specified below)
Death or iUPD immediately after ≥ 2 consecutive missed or non-evaluable disease assessments[2] 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 iCPD or death at time of analysis or lost to follow-up	Date of last evaluable disease assessment	Censored
No tumor assessment at baseline OR No tumor assessment post-first dose, and no death prior to second scheduled post-baseline disease assessment	Date of first dose	Censored

[1] If iUPD is not confirmed and there is no subsequent iSD, iPR or iCR, then the iUPD date should still be used as progression event for PFS in the following scenarios: if the subjects stop study treatment because they were not judged to be clinically stable, or no further response assessments are done; the next timepoint responses are all iUPD, and iCPD never occurs; or the subject dies from their cancer.
[2] Two or more consecutive 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 to allow for a late assessment) 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.

The median and quartiles of PFS and their 95% CIs will be assessed using the Kaplan-Meier method and Brookmeyer and Crowley (1982) method, respectively. The proportion of subjects

that are progression free and alive at 12, 24, 48, 72, 96 weeks and other timepoints of interest and associated 95% CI will be estimated using the Kaplan-Meier method.

8.9.2 PFS based on RECIST 1.1 for solid tumors

PFS based on RECIST 1.1 is defined as time from the first day of treatment to the first documented disease progression (confirmed or not) or death, whichever occurs first. Subjects who have not progressed at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. The censoring guidance and the date of PD/death or censoring are given in the Table 6 below.

Table 6. 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 first 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 tumor assessment at baseline OR No tumor assessment post-first dose, and no death prior to second scheduled post-baseline disease assessment	Date of first dose	Censored
[1] Two or more consecutive 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 to allow for a late assessment) 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.		

The median and quartiles of PFS and their 95% CIs will be assessed using the Kaplan-Meier method and Brookmeyer and Crowley (1982) method, respectively. The proportion of subjects that are progression free and alive at 12, 24, 48, 72, 96 weeks and other timepoints of interest and associated 95% CI will be estimated using the Kaplan-Meier method.

8.9.3 PFS based on RECIL 2017 for Lymphoma

PFS based on RECIL 2017 is defined as time from the first day of treatment to the first documented disease progression (confirmed or not) or death, whichever occurs first. Subjects who have not progressed at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIL assessment. The censoring guidance and the date of PD/death or censoring are the same as that for PFS based on RECIST 1.1.

If data warrants, the median and quartiles of PFS and their 95% CIs will be assessed using the Kaplan-Meier method and Brookmeyer and Crowley (1982) method, respectively. The proportion of subjects that are progression free and alive at 12, 24, 48, 72, 96 weeks and other timepoints of interest and associated 95% CI will be estimated using the Kaplan-Meier method if data warrants.

8.10 Overall Survival

OS is defined as time from the first day of treatment to the date of death. A subject alive at the end of study or lost to follow-up will be censored for OS at the last date when the subject was known to be alive.

The median and quartiles of OS and their 95% CIs will be assessed using the Kaplan-Meier method and Brookmeyer and Crowley (1982) method, respectively. The proportion of subjects alive at 12, 24, 48, 72, 96 weeks and other timepoints of interest and associated 95% CI will be estimated using the Kaplan-Meier method. Summary of OS will be provided for the All Treated population for solid tumors and lymphoma, respectively, if data warrants.

8.11 Statistical Considerations

8.11.1 Adjustments for Covariates

There are no adjustments for covariates in this study.

8.11.2 Handling of Dropouts or Missing Data

For the efficacy variables no imputations will be made for missing values except as noted in considering a NE response.

8.11.3 Interim Analysis and Data Monitoring

No interim analyses for this study.

8.11.4 Multiple Comparison/Multiplicity

No adjustments for multiplicity will be made in this study.

8.11.5 Multicenter Studies

There are no planned analyses to compare differences in response by center.

9. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Separate analysis plans will be provided for PK and PD data.

10. IMMUNOGENICITY ANALYSES

Anti-drug antibodies (ADA) data will be listed and summarized as appropriate.

11. SAFETY ANALYSES

Unless specified otherwise, all safety analyses will be based on the All Treated population. Safety analyses will include MTD evaluation, AEs, laboratory test results (hematology, chemistry, coagulation, thyroid), vital signs and Eastern Cooperative Oncology Group (ECOG).

11.1 Maximum Tolerated Dose Evaluation

The MTD evaluation will be based on the DLT Evaluable Population. The number and percentage of subjects with DLT during the dose escalation phase will be presented by dose level and schedule. The MTD level will be indicated in the summary as appropriate. For single subject cohorts, qualifying ≥ Grade 2 toxicities that trigger a change to at least 3 subject cohorts will also be specified in the table footnotes.

The MTD will be estimated using isotonic regression (based on the DLTs observed in the DLT evaluable subjects). A MAD will be reported if a schedule is fully evaluated, but the DLT rate is less than 25% for all dose levels. 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 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.

11.2 Adverse Events

AE terms on the eCRFs will be mapped to preferred terms (PT) and system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Drug-related AEs are defined as AEs with relationship to study treatment being related or possible related. A worst-case scenario approach will be taken to handle missing data, i.e. AEs with missing relationship to study drug will be treated as drug-related AEs.

All AEs with onset dates on or after the first dose of study treatment are defined as treatment-emergent adverse events (TEAEs). Only TEAEs will be included in AE tables.

If both the start and end dates are completely missing, the AE will be considered treatment-emergent. Partial start and end dates will be imputed similarly as described for prior and concomitant medications in Section 7.7 for the purpose of determining treatment-emergent and AE duration.

The AE summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each SOC based on the total number of subjects. The following summaries will be presented.

- Overall Summary of TEAEs.
- Subject incidence of all TEAEs, drug-related TEAEs, immune related TEAEs by MedDRA SOC, PT and maximum toxicity grade. At each level of subject summarization, a subject is classified to the highest toxicity grade if the subject reported one or more events.
- Subject incidence of all TEAEs, serious TEAE, drug-related TEAEs, and drug-related serious TEAEs by PT.
- Subject incidence of all TEAEs with toxicity grade 3 or 4 by PT.
- DLT for dose escalation cohorts.
- Subject incidence of all TEAEs leading to drug interruptions and permanent discontinuation of study treatment by PT.
- Subject incidence of immune related TEAEs leading to permanent discontinuation of study treatment by PT.
- Subject incidence of deaths within and outside of 30 days of last dose and cause of death.

All AEs, immune related AEs (irAEs), immune related SAEs (irSAEs), drug-related AEs, Grade 3 or 4 AEs, drug-related Grade 3 or 4 AEs, DLTs for dose escalation cohorts, SAEs, fatal AEs, AEs leading to drug interrupted, dose reduced, or drug withdrawal, infusion related reaction signs and symptoms and death will be presented in data listings. Pretreatment AE, defined as AEs that start prior to the first dose of the study treatment, will be flagged in relevant listings. AEs for the Screen Failures population will also be presented in a data listing.

11.3 Clinical Laboratory Evaluation

Laboratory results (hematology, chemistry, coagulation and thyroid) will be summarized for worst case shift from baseline in tables and presented in data listings.

Frequencies of maximum observed Grade 0-4 toxicity, as defined by the NCI CTCAE v5.0, will be presented by laboratory parameter. The analysis will present maximum grade observed. Separate summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate.

All laboratory values will be categorized as "low", "normal", or "high" relative to the normal ranges as data allows. For those laboratory parameters that do not have NCI CTCAE v5.0 grading criteria, worst case shift from baseline to post-baseline will be summarized. If a subject has worst case shifts to both "low" and "high", the subject will be counted in both categories.

Subjects with elevated worst post-baseline Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), total bilirubin, or Alkaline phosphatase (ALP) values that fall into the following categories will be identified and summarized:

- ALT in the categories of <=1x upper limit of normal range (ULN), >1x ULN, >3x ULN;
- AST in the categories of <=1x ULN, >1x ULN, >3x ULN;
- total bilirubin in the categories of <=1x ULN, >1x ULN, >2x ULN
- ALP in the categories of <=1x ULN, >1x ULN, >1.5x ULN, >2x ULN
- Potential Hy's law, defined as at least one case of post-dose total bilirubin > 2 x ULN occurred at the same day or after the first incidence date of ALT or AST > 3 x ULN post treatment.

11.4 Vital Signs

Vital signs and changes from baseline will be presented in a data listing.

11.5 ECOG Performance Status

ECOG performance status scores will be summarized for baseline, and maximum case shift from baseline in a table and presented in a data listing.

12. CHANGE FROM PROTOCOL-SPECIFIED ANALYSES

The following modifications have been made to the protocol-specified analyses:
1. It is clarified in statistical SAP Section 6 that all subjects who have signed the main study ICF are defined as Screened Population, instead of Enrolled Population.
2. It is clarified in SAP Section 6 that the DLT Evaluable Population derivation is for the subjects enrolled in the dose escalation cohorts.

13. 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. Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trial in oncology. Biometrics 2005;61:540-5.
4. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143-e52.
5. Yan F, Mandrekar SJ, Yuan Y. Keyboard: a novel bayesian toxicity probability interval design for phase I clinical trials. Clin Cancer Res 2017;23:3994-4003.

6. Younes A, Hilden P, Coiffier B, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol 2017;28:1436-47.
7. Brookmeyer, R. and Crowley, J. (1982). A confidence interval for the median survival time. Biometrics 38 29-41.

14. APPENDIX: LIST OF TABLES, FIGURES, AND LISTINGS

14.1 List of Tables

ICH Heading	Table Number	Table Description	Analysis Population
14.1		**Demographics**	
	14.1.1	Study Populations and Subject Disposition	All Screened
	14.1.2	Study Treatment Status	All Treated
	14.1.3	Protocol Deviations	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 Treatment	All Treated
14.2		**Efficacy**	
	14.2.1	Objective Response with Confirmation Based on iRECIST for Subjects with Solid Tumors	All Treated
	14.2.2	Objective Response with Confirmation Based on iRECIST for Subjects with Solid Tumors	Efficacy Evaluable
	14.2.3	Objective Response with Confirmation Based on RECIST 1.1 for Subjects with Solid Tumors	All Treated
	14.2.4	Objective Response with Confirmation Based on RECIST 1.1 for Subjects with Solid Tumors	Efficacy Evaluable
	14.2.5	Time to Response and Duration of Response Based on iRECIST for Subjects with Solid Tumors	Efficacy Evaluable
	14.2.6	Time to Response and Duration of Response Based on RECIST 1.1 for Subjects with Solid Tumors	Efficacy Evaluable
	14.2.7	Progression-Free Survival Based on iRECIST for Subjects with Solid Tumors	All Treated
	14.2.8	Progression-Free Survival Based on RECIST 1.1 for Subjects with Solid Tumors	All Treated
	14.2.9	Overall Survival for Subjects with Solid Tumors	All Treated
	14.2.10	Tumor Assessment at Baseline for Subjects with Solid Tumors	All Treated
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 Treatment-Emergent Adverse Events	All Treated
	14.3.1.3	All Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Toxicity Grade	All Treated

ICH Heading	Table Number	Table Description	Analysis Population
	14.3.1.4	Drug-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Toxicity	All Treated
	14.3.1.5	Immune Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Toxicity Grade	All Treated
	14.3.1.6	All Treatment-Emergent Adverse Events by Preferred Term	All Treated
	14.3.1.7	Serious Treatment-Emergent Adverse Events by Preferred Term	All Treated
	14.3.1.8	Drug-Related Treatment-Emergent Adverse Events by Preferred Term	All Treated
	14.3.1.9	Drug-Related Serious Treatment-Emergent Adverse Events by Preferred Term	All Treated
	14.3.1.10	Treatment-Emergent Adverse Events with Toxicity Grade 3 or 4 by Preferred Term	All Treated
	14.3.1.11	Dose Limiting Toxicities	DLT Evaluable
	14.3.1.12	Treatment-Emergent Adverse Events leading to Drug Interrupted by Preferred Term	All Treated
	14.3.1.13	Treatment-Emergent Adverse Events leading to Drug Withdrawn by Preferred Term	All Treated
	14.3.1.14	Immune Related Treatment-Emergent Adverse Events leading to Drug Withdrawn by Preferred Term	All Treated
	14.3.1.15	Deaths	All Treated
14.3.5		**Laboratory**	
	14.3.5.1	Hematology – Maximum CTCAE Grade Shift from Baseline	All Treated
	14.3.5.2	Chemistry – Maximum CTCAE Grade Shift from Baseline	All Treated
	14.3.5.3	Coagulation and Thyroid Function Test – Maximum CTCAE Grade Shift from Baseline	All Treated
	14.3.5.4	Laboratory Tests without CTCAE - Maximum Shift from Baseline with Respect to Normal Range	All Treated
	14.3.5.5	Post-Baseline Potential Serious Hepatoxicity	All Treated
14.3.6		**Other Safety Data**	
	14.3.6.1	ECOG Performance Status – Maximum Shift from Baseline	All Treated
14.3.7		**Immunogenecity**	
	14.3.7.1	SL-279252 Immunogenecity	Immunogenecity

14.2 List of Figures

ICH Heading	Figure Number	Figure Description	Analysis Population
14.2	14.2.1	Horizontal Bar Plot of Duration of Treatment by Response for Subjects with Solid Tumors	All Treated
	14.2.2	Waterfall Plot of Target Lesions Maximum Reduction in Sum of Lesion Diameters for Subjects with Solid Tumors	All Treated
	14.2.3	Plot of Target Lesions Percent Change from Baseline Sum of Lesion Diameters Over Time for Subjects with Solid Tumors	All Treated
	14.2.4	Kaplan-Meier Plot of Duration of Response Based on iRECIST and iRECIST 1.1 for Subjects with Solid Tumors	Efficacy Evaluable
	14.2.5	Kaplan-Meier Plot of Progression-Free Survival Based on iRECIST and RECIST 1.1 for Subjects with Solid Tumors	All Treated
	14.2.6	Kaplan-Meier Plot of Overall Survival for Subjects with Solid Tumors	All Treated

14.3 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 Screened
	16.2.1.2	Study Treatment Discontinuation	All Treated
	16.2.1.3	Informed Consent and Protocol Amendment Re-Consent	All Treated
16.2.2		**Protocol deviations**	
	16.2.2.1	Protocol Deviations	All Treated
	16.2.2.2	COVID-19 Related Protocol Deviations	All Treated
	16.2.2.3	Inclusion and Exclusion Criteria Violations	Screened
16.2.4		**Demographics**	
	16.2.4.1	Demographic and Baseline Characteristics	All Treated
	16.2.4.2	Medical 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 Radiotherapy	All Treated
	16.2.4.6	Prior Surgery Treatment	All Treated
	16.2.4.7	Prior and Concomitant Medications	All Treated
	16.2.4.8	Concomitant Procedures	All Treated
16.2.5		**Study Drug Exposure**	
	16.2.5.1	Study Drug Administration (I)	All Treated

ICH Heading	Listing Number	Listing Description	Analysis Population
	16.2.5.2	Study Drug Administration (II)	All Treated
16.2.6		**Individual efficacy response data**	
	16.2.6.1	Tumor Assessment for Subjects with Solid Tumors: Target Lesions	All Treated
	16.2.6.2	Tumor Assessment for Subjects with Solid Tumors: Non-Target Lesions	All Treated
	16.2.6.3	Tumor Assessment for Subjects with Solid Tumors: New Lesions	All Treated
	16.2.6.4	Tumor Responses Based on iRECIST for Subjects with Solid Tumors	All Treated
	16.2.6.5	Tumor Responses Based on RECIST 1.1 for Subjects with Solid Tumors	All Treated
	16.2.6.6	Tumor Assessment for Subjects with Lymphomas: Target Lesions	All Treated
	16.2.6.7	Tumor Assessment for Subjects with Lymphomas: Non-Target Lesions	All Treated
	16.2.6.8	Tumor Assessment for Subjects with Lymphomas: New Lesions	All Treated
	16.2.6.9	Tumor Responses Based on RECIL for Subjects with Lymphomas	All Treated
	16.2.6.10	Time to Response and Duration of Response for Subjects with Solid Tumors	Efficacy Evaluable
	16.2.6.11	Time to Response and Duration of Response for Subjects with Lymphomas	Efficacy Evaluable
	16.2.6.12	Progression-Free Survival Based on iRECIST for Subjects with Solid Tumors	All Treated
	16.2.6.13	Progression-Free Survival Based on RECIST 1.1 for Subjects with Solid Tumors	All Treated
	16.2.6.14	Progression-Free Survival for Subjects with Lymphomas	All Treated
	16.2.6.15	Overall Survival for Subjects with Solid Tumors	All Treated
	16.2.6.16	Overall Survival for Subjects with Lymphomas	All Treated
16.2.7		**Adverse Event Listings**	
	16.2.7.1	All Adverse Events	All Treated
	16.2.7.2	Dose Limiting Toxicities	DLT evaluable
	16.2.7.3	Drug-Related Adverse Events	All Treated
	16.2.7.4	Adverse Events with Toxicity Grade 3 or 4	All Treated
	16.2.7.5	Drug-Related Adverse Events with Toxicity Grade 3 or 4	All Treated
	16.2.7.6	Fatal Adverse Event	All Treated
	16.2.7.7	Serious Adverse Events	All Treated
	16.2.7.8	Immune Related Adverse Events	All Treated
	16.2.7.9	Immune Related Serious Adverse Events	All Treated
	16.2.7.10	Adverse Events Leading to Drug Interrupted	All Treated
	16.2.7.11	Adverse Events Leading to Dose Reduced	All Treated

ICH Heading	Listing Number	Listing Description	Analysis Population
	16.2.7.12	Adverse Events Leading to Drug Withdrawn	All Treated
	16.2.7.13	Infusion Reaction Signs and Symptoms	All Treated
	16.2.7.14	Death	All Treated
	16.2.7.15	All Adverse Events for Screen Failure Subjects	Screen Failure
16.2.8		**Individual Laboratory Measurements**	
	16.2.8.1	Hematology	All Treated
	16.2.8.2	Clinical Chemistry	All Treated
	16.2.8.3	Coagulation and Thyroid Function	All Treated
16.2.9		**Listing of other safety data**	
	16.2.9.1	Vital Signs and Pulse Oximetry	All Treated
	16.2.9.2	ECOG Performance Status	All Treated
16.2.10		**Immunogenecity**	
	16.2.10.1	SL-279252 Immunogenecity	Immunogenecity