Protocol Title: 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

Short Title: Phase 1 Study of SL-279252 (PD1-Fc-OX40L) in Subjects with Advanced Solid Tumors or Lymphomas

Protocol Identifying Number: SL01-DEL-101

Version Number: v07

Compound Number: SL-279252

Study Phase: Phase 1

Investigational New Drug (IND) Sponsor: Shattuck Labs

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Regulatory Agency Identifier Number(s)

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Approval Date: 12 July, 2021

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_00	05 November 2018	Original
SL01-DEL-101_01	19 December 2018	Amendment No. 1

Rationale for Amendment 01 Changes

The protocol is amended to address comments provided by the United States Food and Drug Administration to the original protocol submitted with the IND Application

Summary of Changes

1. The upper bound of the target DLT range was changed to 33%.
2. The Dose Expansion cohorts may be opened to enroll subjects in parallel with the Dose Escalation cohorts. Clarified that only dose levels that have been cleared for safety (permitted to escalate per the Keyboard Design rules) with a minimum of 6 subjects treated at that dose level can be expanded.
3. Since Grade 3 cytokine release syndrome (CRS) requires dose reduction and may result in discontinuation of investigational product (IP), the protocol was modified to include Grade ≥3 CRS as a DLT.
4. Modified the protocol's guidance for CRS to ensure subject safety:

   For any grade CRS

   a. Subjects will be admitted for close observation.

   For Grade 2 CRS

   b. All doses of IP are held until CRS has returned to Grade ≤1 for at least 3 days.
   c. Following a Grade 2 CRS event, the next two doses of SL-279252 must be administered in an inpatient setting.
   d. For continued treatment following a Grade 2 CRS event, subjects will be admitted to hospital for close observation until resolution of symptoms.

   For Grade 3 CRS

   e. All doses of study medication are held until symptoms have returned to grade ≤1 for at least 3 days. If the decision is made to continue treatment following resolution, the dose of SL-279252 must be reduced one dose level and premedication with high dose steroids must be administered prior to the first dose following Grade 3 CRS event. The next two doses of SL-279252 must be administered with appropriate inpatient monitoring (e.g., observation for 24 hours following infusion when receiving premedication).
   f. Any subject that experiences recurrence of Grade 3 CRS following re-treatment must be permanently discontinued from study treatment.

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_00	05 November 2018	Original
SL01-DEL-101_01	19 December 2018	Amendment No. 1

5. The protocol was modified so that dose escalation between the second and third dose levels is a half-log increment (i.e., 0.0001 mg/kg, 0.001 mg/kg, 0.003 mg/kg, 0.01 mg/kg, etc. instead of a log increment i.e., 0.0001 mg/kg, 0.001 mg/kg, 0.01 mg/kg, etc.)
6. Modified dose escalation scheme such that dose level 9 corresponds to a dose of 3.0 mg/kg of SL-279252 and dose level 10 corresponds to a dose of 6.0 mg/kg of SL-279252
7. Modified ADA sampling schedule so that subjects who test positive for ADA while on study or within 7-30 days after receiving their last dose of SL-279252 will undergo periodic testing for ADA until levels return to baseline.

Administrative Changes (28-March 2019):

1. Added the EUDRACT and NCT numbers to the protocol title page and removed other as an option for adding another numeric identifier of the protocol.
2. Corrected protocol number from SL01-DEL-01 to SL01-DEL-101 in the header of the summary of changes header.
3. No content changes were made to the protocol.

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_00	19 December 2018	Amendment No. 1
SL01-DEL-101_01	18 June 2019	Amendment No. 2

Rationale for Country-specific Amendment 02 for Belgium

The protocol is amended to address comments provided by the Belgium Regulatory Authority to Amendment 01 of the protocol.

Summary of Changes

1. Removed the barrier method of contraception as an option for female subjects of child bearing potential. This method, of contraception does not meet criteria of <1% failure rate for preventing pregnancy.
2. SL-279252 treatment may induce cytokines including IL-6 which can inhibit the activity of cytochrome P450 (CYP450) enzymes as described in the literature (Evers et al., 1013, Drug Metabolism and Disposition). A cautionary medications section was added to the protocol to address a potential drug-drug interaction of SL-279252 with concomitant medications that are CYP450 substrates. SL-279252 may induce cytokine release and coincidentally increase blood levels of drugs that are CYP450 substrates.

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_01	19 December 2018	Amendment No. 1
SL01-DEL-101_03	11 October 2019	Amendment No. 3

Rationale for Amendment 03

The protocol is amended to include changes requested by the Belgium Regulatory Authority into the global protocol for consistency across the study. Amendment 02 was a country-specific amendment for Belgium. The summary of changes for Amendment 02 are provided in Appendix 16.10. Additionally, Amendment 03 incorporates pharmacodynamic cohorts during Dose Escalation, in order to obtain additional pharmacodynamic data at a dose level that has previously completed evaluation for safety and has not exceeded the MTD. Collection of additional blood samples for receptor occupancy and immunophenotyping has been added in Cycle 1 (receptor occupancy in dose expansion cohorts) and Cycle 2 (receptor occupancy and immunophenotyping in all subjects) to characterize pharmacodynamics at time points that will be helpful to inform the recommended phase 2 dose and schedule. Minor changes to the study objectives and statistical plans are made to clarify planned analyses. Editorial changes are included to remove unclear text or further clarify text (e.g., definitions of study populations, etc), and for consistency. Sample size estimates, objectives and endpoints, biomarker sample collection time points and other modifications are included to account for additional pharmacodynamic and other planned study assessments.

Summary of Changes for Global Amendment

1. Amendment 02 changes included for countries outside of Belgium
2. Pharmacodynamic cohorts are now included for enrollment during dose escalation.
3. Editorial changes to remove unclear text and to further clarify intent of study plans are provided throughout the document to statistical plans, definitions of study populations, etc).
   a) Time to tumor response added as an endpoint for assessment of antitumor activity,
   b) Minor response removed for subjects with lymphoma as part of the clinical benefit rate definition;
   c) iSD as part of clinical benefit rate defined as ≥16 weeks duration instead of ≥12 weeks
   d) Refined definitions of populations under study in statistical section
   e) Revised sample size estimates to accommodate the addition of pharmacodynamic cohorts for enrollment during dose escalation
   f) Clarification of MTD selection based on isotonic estimate
4. Receptor occupancy samples will also be collected in dose expansion cohorts (no longer limited to collection in dose escalation cohorts).
5. Additional time points for collection of biomarker samples (immunophenotyping and receptor occupancy) in cycle 2 on days 15 and 16 have been added that impact schedule of assessment and supplementary tables for dose escalation and dose expansion cohorts.

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_03	11 October 2019	Amendment No. 3
SL01-DEL-101_04	24 February 2020	Amendment No. 4

Rationale for Amendment 04

Revised eligibility criteria and tumor types included for study participation. The summary of changes are provided in Appendix 16.12.

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_04	24 February 2020	Amendment No. 4
SL01-DEL-101_05	1 October 2020	Amendment No. 5

Rationale for Global Amendment 05

The main purpose for this amendment is to revise eligibility criteria and tumor types included for study participation. The dosing day window for administration of SL-279252 was clarified in the Schedule of Assessment (SOA) tables. The dose escalation plan table was revised to include infusion time windows for administration of SL-279252. In addition, predose, end of infusion (EOI) and 6 hour post EOI PK sample time points were added for collection on C4/D1 to confirm clearance and half-life parameters with repeat dosing of SL-279252. Language was added that clarifies protocol procedures to follow for assessment of AE severity and for recording and reporting AEs. Minor editorial text changes are also included with this amendment.

The Summary of Changes for Global Amendment 05 is provided in Appendix 16.13

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_05	1 October 2020	Amendment No. 5
SL01-DEL-101_06	4 February 2021	Amendment No. 6

Rationale for Global Amendment 06

The main purpose for this amendment is to revise exclusion criterion #2 to provide an exception for subjects with uveal melanoma, to clarify language about ad hoc samples to be collected if an infusion-related or cytokine release adverse reaction occurs, and to clarify the DLT-evaluable population for subjects receiving SL-279252 therapy on Schedule 2.

The Summary of Changes for Global Amendment 06 is provided in Appendix 16.14

Shattuck Labs Document Number	Date	Version
SL01-DEL-101_06	4 February 2021	Amendment No. 6
SL01-DEL-101_07	12 July 2021	Amendment No. 7

Rationale for Global Amendment 07

The main purpose for this amendment is to institute the requirement that eligible subjects have tumors with PD-L1 expression ≥1% according to tumor proportion score (TPS) or combined proportion score (CPS). PD-L1 is a target of the PD1 portion of bifunctional fusion protein SL-279252. Restricting enrollment to subjects whose tumors demonstrate expression of PD-L1 may improve the likelihood of subject benefit. In addition, subjects with uveal or ocular melanoma are ineligible for participation.

The description of the drug product is changed to remove reference to a 1 mL fill volume since a larger fill volume is planned to ease dose preparation. Drug product fill volumes will be described in the Study Pharmacy Manual. The length of time to thaw a vial is also removed since it is obvious when the frozen solution is completely thawed and the time will vary based on fill volume.

Minor editorial changes were made to clarify study conduct procedures during dose escalation and requirements for collection of ad hoc labs if IRR and/or CRS occur.

The Summary of Changes for Global Amendment 07 are provided in Appendix 16.15.

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LIST OF ABBREVIATIONS

Ab	Antibody
AchR	Acetylcholine receptor
ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANCA	Anti-neutrophil cytoplasmic antibodies
APTT	Activated partial thromboplastin time
APC	Antigen presenting cell
AR	Adverse reaction
ARC	Agonist redirected checkpoint
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
AUC	Area under the serum concentration time curve
$AUC_{0\text{-last}}$	Area under the serum concentration time curve, time 0 to the last quantifiable concentration
$AUC_{0\text{-inf}}$	Area under the serum concentration time curve from time 0 extrapolated to infinity
$AUC_{0\text{-t}}$	Area under the serum concentration time curve, time 0 to time = t
$\%AUC_{ext}$	Percentage of AUC0-inf due to extrapolation from Tlast to infinity
AUCtau	The area under the serum concentration time curve, over the dosing interval
BAL	Bronchoalveolar lavage
β-hCG	Beta- human chorionic gonadotropin
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit rate
CD	Cluster of differentiation
C	Celsius
C1D1	Cycle 1, day 1
cfNA	Cell-free or circulating nucleic acids (note: tumor-associated)
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CK-MB	Creatine kinase-muscle/brain
CL	Clearance
Cm	Centimeters
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CMP	Clinical monitoring plan
CNS	Central nervous system
CO_2	Bicarbonate
CPS	Combined proportion score
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract Research Organization

CRP	C reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CTLA-4	Cytotoxic T cell lymphocyte-associated antigen 4
CV	Coefficient of variation
CYP450	Cytochrome P450
D1/D8/D15/D22 etc.	Day 1/ Day 8/ Day 15/ Day 22 etc.
dL	Deciliter
DL	Dose level
DLT(s)	Dose-limiting toxicity(ies)
DM	Diabetes mellitus
DMARD	Disease- modifying antirheumatic drug
DNA	Deoxynucleic acid
DOR	Duration of response
DRF	Dose-range-finding
EC50	Half maximal effective concentration
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of infusion
ESR	Erythrocyte sedimentation rate
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin-fixed paraffin-embedded
FP	Fusion protein
FSH	Follicle stimulating hormone
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GEJ	Gastro-esophageal junction
GI	Gastrointestinal
GITR	Glucocorticoid-induced TNFR
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage colony stimulating factor
H1/H2	Histamine 1/ Histamine 2
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HL	Hodgkin’s lymphoma
HNSCC	Head and neck squamous cell carcinoma
HNSTD	Highest non-severely toxic dose
hr (time)	Hour(s)
HR	Heart rate
HSR(s)	Hypersensitivity reaction(s)
IB	Investigator’s brochure

iBOR	Immune response evaluation criteria in solid tumors best overall response
ICF	Informed consent
ICH	International Conference of Harmonisation
iCPD	Immune confirmed progression of disease
iCR	Immune complete response
ICU	Intensive care unit
ID	Identification
IEC	Institutional Ethics Committee
IFNγ	Interferon gamma
IHC	Immunohistochemistry
IL	Inteleukin
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
iPR	Immune partial response
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune response evaluation criteria in solid tumors
IRR(s)	Infusion-related reaction(s)
irSAE	Immune-related serious adverse event
iSD	Immune stable disease
ITIM	Immunoreceptor tyrosine-based inhibition motif
iUPD	Immune unconfirmed progression of disease
IV (i.v.)	Intravenous
IVIG	Intravenous immunoglobulin
Kd	Receptor off-rate constant
Kg	Kilogram
L	Liter
LAG-3	Lymphocyte activation gene 3
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
m^2	Square meter
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
MMF	Mycophenolate mofetil
Mmol	Millimole
MMRD	Mismatch repair deficient
MR	Minor response
MRI	Magnetic resonance imaging
MSI/ MSI-H	Microsatellite instability / microsatellite instability high
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NHP	Non-human primate
Ng	Nanogram

NIF/VC	Negative inspiratory force / vital capacity
NL(s)	New lesion(s)
NLNT	New lesions non-target
NLT	New lesions target
nM	Nanomolar
NSAIDS	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OX40	TNFRSF4, also known as CD134 / OX40 receptor
OX40L	Ligand for OX40 receptor, also known as CD252
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1 / PD-L2	Programmed cell death ligand 1 / Programmed cell death ligand 2
PFT	Pulmonary function test
PK	Pharmacokinetic
pM	Picomolar
PR	Partial response
PS	Performance status
PSPD	Pseudo-progression of disease
PT	Prothrombin time
PTU	Propylthiouracil
QID	*Quarter in die* (4 times per day)
QTc	Corrected QT interval
RBC	Red blood cell
RCC	Renal cell cancer
RECIL	Response evaluation criteria in lymphoma
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
SCCA	Squamous cell carcinoma of the anal canal
scFv	Single-chain variable fragment
SD	Stable disease
SEB	Staphylococcal enterotoxin B
Skin-SCC	Squamous cell carcinoma of the skin
SL-279252	PD1-Fc-OX40L agonist redirected checkpoint
SLM	Study Lab Manual
SMC	Safety Monitoring Committee
SOA	Schedule of Assessments
SOI	Start of infusion
SOM	Sum of measurements
SPM	Study Pharmacy Manual
SRM	Study Reference Manual
SUSAR	Suspected, unexpected serious adverse reaction
T	Temperature
T3/T4	Thyroxine 3/thyroxine 4
t½	terminal elimination half-life
TB	Tuberculosis

TCR	T cell receptor
TFTs	Thyroid function tests
TGF	Tissue growth factor
TID	*Ter in die* (3 times per day)
TIGIT	T-cell immunoglobulin and ITIM Domain
TIM-3	T cell immunoglobulin mucin 3
TK	Toxicokinetic
T_{last}	Time of last observed quantifiable concentration
TLS	Tumor lysis syndrome
T_{max}	Time of maximum observed concentration
TMB	Tumor mutational burden
TMDD	Target-mediated drug disposition
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor alpha
TNFR	Tumor necrosis factor receptor
TNFSF	Tumor necrosis factor receptor superfamily
TPO	Thyroid peroxidase
TPR	Time point response
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
TTR	Time to response
Txt	Treatment
µg	Microgram
ULN	Upper limit of normal
UP	Unanticipated problems
USPI	United States Prescribing Information
Vz	Volume of distribution
WBC	White blood cell
Wk	Week
λz	Terminal elimination rate constant
~	Approximately
º	Degree

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable Federal Regulations on the Protection of Human Subjects. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

_____ _____

Print/Type Name Signature

Date: _____

KEY TRIAL CONTACTS

Medical Monitor Name and Contact Information is provided in the Study Reference Manual

Sponsor Signatory:

[redacted]

[redacted]
Date

Chief Medical Officer, Shattuck Labs

PROTOCOL SYNOPSIS

Sponsor	Shattuck Labs
Product Name	SL-279252
Other Names	PD1-Fc-OX40L recombinant fusion glycoprotein
Protocol Title	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
Protocol Number	SL01-DEL-101
Clinical Phase	Phase 1
Planned Sample Size	Approximately 78 to 93 subjects
Planned Number of Sites & Countries	8-10 clinical sites; United States, Canada, Belgium and Spain
Recruitment Duration:	24 months (2 years)
Study Duration	32 months (< 3 years)

Background and Rationale

The investigational product (IP), SL-279252, is a first-in-class agonist redirected checkpoint (ARC) fusion protein (FP) consisting of the extracellular domains of human programmed cell death 1 (PD- 1) and OX40L, linked by a central Fc domain (PD1-Fc-OX40L). The mechanism of action of SL-279252 is designed to intercept one of the key immunosuppressive pathways within the tumor microenvironment (TME): the PD-1 – programmed cell death ligand 1/programmed cell death-ligand 2 axis (PD-L1/PD-L2). SL-279252 can bind to PD-L1 and PD-L2 expressed on tumor and antigen presenting cells, and replace that inhibitory signal with OX40L, resulting in an incoming T cell experiencing co-stimulation via engagement through its OX40 receptor instead of suppression through PD-1 interactions. Importantly, because the extracellular domains (ECDs) of PD-1 and OX40L are physically linked to one another and localized to the TME, tumor infiltrating T cells will receive co-stimulation at the same time they recognize a tumor antigen via the T cell receptor (TCR).

SL-279252 is able to bind with high affinity to both targets simultaneously and stimulate anti-tumor T cell activity. The PD-1 end of the fusion protein binds PD-L1 and PD-L2 with affinities of 2.08 and 1.76 nM, respectively, and the OX40L end binds OX40 with an affinity of 246 pM. The PD-1 domain efficiently outcompetes PD-L1 blocking antibodies for ligand binding, and the OX40L domain potently stimulates OX40-mediated nuclear factor kappa B signaling in a luciferase-based reporter assay. When activated human T cells were co-cultured with PD-L1 positive human tumor cells, SL-279252 enhanced proliferation of T cells and production of interleukin (IL)-2, interferon-gamma (IFNγ) and tumor necrosis factor alpha (TNF-α), which led to efficient killing of tumor cells.

SL-279252 was compared to sequence equivalents of nivolumab, pembrolizumab and tavolixizumab in several in vitro functional assays using human lymphocytes in the presence of Staphylococcal enterotoxin B (SEB): higher concentrations of cytokines were released with SL- 279252 than with the antibodies alone or in combination with one another. The murine version of SL-279252 (mPD1-Fc-OX40L) was studied head-to-head with mouse PD-1/L1 and

Background and Rationale (continued)
OX40 antibodies both alone and in combination and led to improved tumor control and rejection rates as compared to the antibody combinations in multiple models.

SL-279252 is a pharmacologically active molecule. In the non-human primate (NHP) studies, dose-dependent infusion-related reactions (IRRs) were the primary toxicity of concern. These adverse reactions were immune-mediated and multifactorial in etiology consistent with target-mediated pharmacology of SL-279252 as well as immunogenicity (anti-drug antibodies (ADA), complement activation) related effects. Collectively, the effects at 40 and 80 mg/kg/dose were considered adverse and the effects at 10 mg/kg/dose were not considered adverse. The highest non-severely toxic dose (HNSTD) of SL-279252 was determined to be 10 mg/kg.

The preclinical and nonclinical data collectively suggest that SL-279252 has unique immunological properties, with the potential for anti-tumor activity. This first-in-human, Phase 1 trial will assess the safety, tolerability, PK, pharmacodynamics and anti-tumor activity of SL-279252 in subjects with tumor types that have been documented to respond to anti-PD-1/PD-L1 therapy. All subjects enrolled in this trial are required to have received or been intolerant to standard of care therapies. The majority of subjects will also have received PD-1/L1 and/or cytotoxic T cell lymphocyte-associated antigen 4 (CTLA-4) inhibitors and progressed.

Study Objectives

Primary Objectives	**Outcome Measures**
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	**Outcome Measures**
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.

Secondary Objectives	Outcome Measures
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);
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	**Outcome Measures**
Dose Escalation and Dose Expansion: To assess target engagement 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.

Exploratory Objectives	Outcome Measures
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 explore additional measures of anti-tumor activity of SL-279252	• Duration of response (DOR): time between first response (iCR or iPR, whichever is recorded first) and date of disease progression) • Time to response (TTR): time from the start of treatment with SL-279252 to the first objective tumor response (iCR or iPR, whichever is recorded first) • Progression free survival: time from first dose of SL-279252 to progression or death, whichever comes first • Overall survival: time from first dose of SL-279252 to death
Dose Escalation and Dose Expansion : To explore relationship between PK/pharmacodynamics and the relationship between PK and clinical activity including tumor growth kinetics	PK/pharmacodynamics and clinical activity outcomes as described above
Study Design	
This is a Phase 1 first in human, open label, multi-center, 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. The study design consists of Dose Escalation (Section 3.2) and Dose Expansion Cohorts (Section 3.3). In the dose escalation phase of the study, subjects will be enrolled into sequential dose levels (DL) as outlined in Section 3.2.4 and Table 5. Enrollment into a DL cohort will follow the Keyboard Design outlined in the Appendix, Section 16.3 [Yan, 2017]. During dose escalation, two possible schedules (Schedule 1 and Schedule 2) for administration of SL-279252 may be explored as outlined in Section 3.2.4. Schedule 1 will be evaluated first. A transition to Schedule 2 may be implemented for reasons outlined in 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 support less frequent dosing of SL-279252 (e.g., one dose given every two weeks or every three weeks or every four weeks).

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. The primary objective of the expansion phase is to further refine the safety and tolerability of SL-279252. One or two expansion cohorts will evaluate doses of SL-279252 using one selected schedule. At the end of dose escalation and dose expansion, safety, PK, anti-tumor activity, and pharmacodynamic data will be reviewed to identify the RP2D.

Treatment Schedule

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

- *Schedule 1*: will determine the safety of 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*: will determine the safety of 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) may be investigated if safety data from Schedule 1 indicate this approach is most prudent

Dose Escalation Scheme

Dose Level	Dose of SL-279252 (mg/kg)[a,b,c,d]	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 will 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 (See Sections 5.2.3 and 5.4 for details)

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.

Definition of Dose Limiting Toxicity

Dose limiting toxicities (DLTs) are defined in the bulleted points below. Toxicities will be graded as per NCI CTCAE v5. The determinate period for DLT is the first 21 days or 28 days of treatment on Schedule 1 or Schedule 2, respectively. However, there is provision in the criteria below for toxicities that occur beyond this period to be considered in the definition of the RP2D. **Note**: Toxicities clearly related to disease progression or intercurrent illness are not considered DLTs. Inflammatory reactions attributable to local anti-tumor responses (e.g., severe pain) are not considered DLTs.

- Any Grade 4 irAE
- Elevations in liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and/or total bilirubin:
  - In subjects who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN); AST or ALT elevation of >8 x ULN or total bilirubin > 5 x ULN
  - In subjects who enroll with AST/ALT/total bilirubin > ULN; AST or ALT elevation of >8 x baseline or total bilirubin > 5 x baseline
  - Evidence of Hy's Law (AST or ALT > 3 x ULN [or baseline*] with concurrent increase in total bilirubin > 2 x ULN [or baseline*] without evidence of cholestasis or alternative explanation such as disease progression or viral hepatitis; *ULN or baseline dependent on value at enrollment as described above.
- Any Grade 3 irAE that requires permanent discontinuation of SL-279252
- Any other Grade 3 irAE with the following exceptions:
  - Grade 3 skin toxicity that downgrades to Grade 2 or less within 7 days with optimal supportive care
  - Grade 3 hypothyroidism, hyperthyroidism, or hyperglycemia that can be managed with treatment
  - Grade 3 diarrhea with no evidence of colitis that resolves within 72 hours with appropriate clinical management
- The following Grade 2 irAEs:
  - Grade 2 ocular toxicity requiring systemic steroids
  - Grade 2 cardiotoxicity that requires permanent discontinuation of SL-279252
  - Grade 2 Guillain-Barre Syndrome
- Any Grade 3 or greater non-irAE **except** for those listed below:
  - Grade 3 fatigue lasting ≤ 7 days
  - Grade 3 or 4 neutropenia not associated with fever that improves to Grade 2 within 7 days
  - Grade 3 or 4 lymphopenia
  - Grade 3 thrombocytopenia not associated with clinically significant bleeding and that does not require medical intervention
  - Grade 3 electrolyte abnormalities that are not associated with clinical signs/symptoms and are reversed with appropriate medical intervention
  - Grade 3 or 4 amylase and/or lipase abnormalities that are not associated with clinical signs/symptoms or finding on imaging consistent with pancreatitis

Definition of DLT (continued)

- Grade 3 vomiting and/or Grade 3 nausea that resolves within 72 hours with appropriate clinical management

- Other toxicities may be considered a DLT as determined by the investigator in conjunction with the Safety Monitoring Committee (SMC)

A Grade ≥ 3 AE that occurs beyond the DLT period (21 days for schedule 1 or 28 days for schedule 2) or Grade 2 events that require continuous interruption of SL-279252 for more than 6 weeks or toxicities that result in subjects not receiving at least 66% of the scheduled dose during the DLT assessment period may be taken into consideration when assessing the totality of the data in determining evaluability for DLT and the RP2D.

Eligibility Criteria

Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply.

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.
2. Subject has a histologically confirmed diagnosis of one of the following unresectable locally advanced or metastatic malignancies: melanoma, non-small cell lung cancer (squamous, adeno, or adeno-squamous), urothelial cancer, squamous cell carcinoma of the head and neck, squamous cell cervical cancer, gastric or gastro-esophageal junction adenocarcinoma, squamous cell carcinoma of the anal canal, squamous cell carcinoma of the skin, renal cell cancer, Hodgkin's lymphoma, and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding CNS malignancies. MSI and MMRD testing results as per institution is acceptable.
   - Head and neck cancers: Subjects must have primary tumor locations in the oropharynx, oral cavity, hypopharynx, or larynx. Primary tumor sites of nasopharynx, maxillary sinus, paranasal, and unknown primary are excluded.
   - Non-small cell lung cancers: Subjects with a known EGFR sensitizing (activating) mutation or an ALK fusion are excluded.
   - Melanoma: Subjects with a diagnosis of uveal or ocular melanoma are excluded.
3. Eligible subjects must have tumors expressing PD-L1 ≥1% by tumor proportion score (TPS) or combined proportion score (CPS) as determined by a local laboratory.
   - This criteria does not apply to subjects with a diagnosis of melanoma, renal cell carcinoma, Hodgkin's lymphoma and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors.
4. Subject must have received, been intolerant to, or is ineligible for standard therapy (per local guidelines and approvals) or have a malignancy for which there is no approved therapy considered standard of care.
5. Age 18 years and older.
6. Has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.
7. Has measurable disease by iRECIST (solid tumors) or RECIL 2017 (lymphoma). Refer to Appendix Sections 16.6 and 16.7 for details on criteria of measurable disease.
8. Has life expectancy of greater than 12 weeks.

9. Laboratory values must meet the following criteria.

Laboratory parameter	Threshold value
• Absolute lymphocyte count (ALC)	≥ 0.8 x 10^9/liter (L)
• Absolute neutrophil count (ANC) without growth factor support	≥ 1.5 x 10^9/L
• Platelet count	≥ 50 x 10^9/L
• Hemoglobin (Hgb) with no blood transfusions for at least 5 days prior to D1 of investigational product (IP; SL-279252)	> 9.0 g/dL
• Creatinine clearance (CrCl)	≥ 30 milliliter (mL)/min (modified Cockcroft-Gault)
• ALT/AST	≤ 3 x ULN
• Total bilirubin subjects with isolated indirect hyperbilirubinemia are permitted if direct bilirubin ratio is <35% and total bilirubin is ≤ 3.0 x ULN	≤ 1.5 x ULN;
• Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) ≥ lower limit of normal (LLN) per institutional threshold. If LLN is not defined for a given institution, then ejection fraction must be ≥50 %.	

10. Females of child bearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of D1 of IP. NOTE: FCBP unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally postmenopausal for at least 12 consecutive months (see Appendix Section 16.2 for additional details). Documentation of postmenopausal status must be provided. FCBP should use an acceptable method of contraception (see Appendix Section 16.2) to avoid pregnancy during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of IP. FCBP must start using acceptable contraception at least 14 days prior to D1 of IP.
11. Male subjects with female partners must have azoospermia from a prior vasectomy or underlying medical condition or agree to use an acceptable method of contraception during treatment and for 30 days (which exceeds 5 half-lives) after last dose of SL-279252 (see Appendix Section 16.2). Male subjects of reproductive potential must start using acceptable contraception at least 14 days prior to D1 of treatment with SL-279252 as per Appendix Section 16.2.
12. All AEs resulting from prior anti-cancer immunotherapy have resolved (NOTE: exceptions include alopecia, vitiligo, and endocrinopathies adequately treated with hormone replacement).
    - Subjects that were discontinued from prior PD-1/L1 therapy due to immune-related adverse events are not eligible
13. Recovery from toxicities from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (NOTE: Low-grade toxicities (e.g., alopecia, ≤ Grade 2 lymphopenia, ≤ Grade 2 hypomagnesemia, ≤ Grade 2 neuropathy) may be allowed at the discretion of the investigator if considered clinically insignificant. Please consult the Sponsor Medical Monitor to discuss these cases).

Eligibility Criteria

Exclusion Criteria
Participants are excluded from the study if any of the following criteria apply:

1. Has received more than two prior checkpoint inhibitor containing treatment regimens (regimen refers to either monotherapy or combination immunotherapies) or has had prior treatment with an OX40 agonist.
    - Prior PD-1/L1 therapy is not required.
2. Refractory to last PD-1/L1 inhibitor-based therapy which is defined as disease progression within 3 months of treatment initiation.
    - Subjects must have had clinical benefit (stable disease or response) to last PD-1/L1 inhibitor-based therapy for at least three months to be eligible.
    .
3. Any anti-cancer therapy within the time intervals noted below prior to first dose (D1) of SL-279252.

Therapy	**Washout period**
Chemotherapy	3 weeks
Hormonal therapy	3 weeks
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	3 weeks
Tumor vaccine	4 weeks
Cell-based therapy	8 weeks
Other mAbs or biologic therapies	3 weeks
Major surgery	2 weeks
Radiation (except palliative intent which does not require washout)	2 weeks

4. Concurrent chemotherapy, immunotherapy, biologic or hormonal therapy is prohibited. Concurrent use of hormones for non-cancer related conditions is acceptable.
5. Use of corticosteroids or other immunosuppressive medication, current or within 14 days of D1 of IP with the following exceptions (i.e., the following are allowed during treatment with or within14 days of D1 of IP):
    - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
    - Physiological doses of replacement steroid (e.g., for adrenal insufficiency) provided ≤ 10 mg/day of prednisone or equivalent
    - Steroid premedication for hypersensitivity reactions (HSRs; e.g., reaction to IV contrast)
6. Receipt of live attenuated vaccine within 28 days of D1 of IP.
7. Active or documented history of autoimmune disease (autoimmune disease does not refer to irAEs; for irAEs see inclusion criteria #11). Exceptions include Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.
8. Active pneumonitis (i.e. drug-induced, idiopathic pulmonary fibrosis, radiation-induced, etc.).
9. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of IP).
10. Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious gastrointestinal (GI) disease associated with diarrhea within 6 months of D1 of IP.
11. Clinically significant or uncontrolled cardiac disease including any of the following:
    - Myocarditis
    - Unstable angina within 6 months from D1 of IP
    - Acute myocardial infarction within 6 months from D1 of IP
    - Uncontrolled hypertension
    - New York Heart Association (NYHA) Class II, III or IV congestive heart failure

- Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy)

12. Untreated central nervous system (CNS) or leptomeningeal metastases. Subjects with treated CNS metastases must have completed definitive treatment (radiotherapy and/or surgery) > 2 weeks prior to D1 of IP and no longer require steroids.
13. Women who are breast feeding.
14. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or compromised ability to provide written informed consent.
15. Another malignancy that requires active therapy and that in the opinion of the investigator and Sponsor would interfere with monitoring of radiologic assessments of response to IP.
16. Has undergone allogeneic stem cell transplantation or organ transplantation.
17. Known history or positive test for human immunodeficiency virus, or positive test for hepatitis B (positive for hepatitis B surface antigen [HBsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).
    - (NOTE: Hepatitis B virus (HBV): Subjects who are hepatitis B core antibody [HBcAb] positive, but HBsAg negative are eligible for enrollment. HCV: Subjects who are HCV Ab positive, but HCV RNA negative are eligible for enrollment).

Safety Oversight

Study progress and safety will be reviewed throughout the conduct of the study. Periodic safety reviews (once a month or more frequently if required) will be undertaken by the Safety Monitoring Committee (SMC) consisting of study investigators and Sponsor representatives. Available safety data for all subjects at the time of scheduled meetings will be reviewed and summarized. Based on the severity of the toxicities, indicators of potential anti-tumor activity, and other factors, a recommendation whether to modify the dose and/or study or continue enrollment will be made by the Sponsor collaboratively with input from the SMC. Regulatory authorities and IRBs/IECs will be notified of any decisions to halt the study or subject enrollment.

Statistics

Frequency tables will be used to describe safety and tolerability parameters such as: AEs, irAEs, SAEs, fatal SAEs and irAEs leading to discontinuation of SL-279252. During dose escalation, DLTs will be tabulated by dose level (within each schedule if applicable). Following the Keyboard design, the MTD will be estimated using isotonic regression (based on the DLTs observed in evaluable subjects) or the MAD will be reported if the DLT rate never reaches the target range of 25-33.3%. During dose expansion, continuous toxicity monitoring using sequential boundaries will be used to specifically monitor IRR and toxicities leading to discontinuation of SL-279252.

1. INTRODUCTION, BACKGROUND AND STUDY RATIONALE

1.1 Background Information

The human immune system can prevent the initiation of cancer through constant immune surveillance or immunoediting, whereby nascent transformed cells are recognized by the immune system and eliminated, often preventing tumor outgrowth and metastasis [Schreiber, 2011; Muenst, 2016]. When cancer does arise, immunoediting results in an adaptive response within tumors, and the tumor microenvironment (TME), to co-opt endogenous immune suppressive pathways that provide an extrinsic survival advantage to the tumor cells through inhibition of the immune system. Thus, cancers avoid immune surveillance and destruction through multiple mechanisms including (but not limited to) downregulation of costimulatory signals required for lymphocyte activation, and upregulation of inhibitory signals essential for preventing autoimmunity, thereby circumventing the immune system's ability to recognize tumor cells. Immune evasion is therefore an extrinsic hallmark of cancer, just as pro-survival or pro-growth mutations in tumor suppressor genes or oncogenes, respectively, are intrinsic hallmarks of cancer [Hanahan, 2011]. Advancements in our understanding of the mechanisms responsible for cancer immune evasion has led to the development of therapies that have shown promise in overcoming tumor-mediated immune suppression.

In general, cancer immunotherapy encompasses a broad spectrum of approaches that either target tumor cells directly (e.g., monoclonal antibodies [mAbs], radioimmunotherapy, antibody drug conjugates, and immunotoxins/oncolytic viruses) or activate immune cells to kill cancer cells (e.g., vaccines, cellular therapies, checkpoint antagonists and stimulatory agonists) [Sathyanarayanan, 2015]. Recent strategies in immunotherapy have focused on therapeutic interventions that modulate pathways governing T cell activation to overcome cancer immune evasion. For example, checkpoint antagonists, or immune checkpoint inhibitors, are agents that block receptors or ligands involved in attenuating T cell activation. Stimulatory agonists are agents that engage co-stimulatory pathways and immune receptors and lead to the activation and proliferation of T cells. Over the past decade, pharmaceutical research efforts have focused intently on developing immunotherapy drugs that either inhibit immune checkpoint molecules responsible for T cell anergy or stimulate tumor necrosis factor receptor (TNFR) pathways linked to T cell activation.

The cytotoxic T cell lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathways are major negative regulators of T cell receptor (TCR) signaling. These pathways are engaged by tumor cells to avoid immune surveillance by T cells. Targeted inhibitors of CTLA-4, PD-1 or PD-ligand (L)1 are immune checkpoint inhibitors that have demonstrated efficacy in many tumor types [Postow, 2015]. Moreover, since multiple inhibitory receptors and soluble factors are involved in T cell exhaustion in the TME apart from PD-1 and CTLA-4, such as T cell immunoglobulin mucin 3 (TIM-3), lymphocyte activation gene 3 (LAG-3) protein, and the T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif (ITIM) domain (TIGIT) protein among others; a surge in pre-clinical/clinical development of these next generation-checkpoint inhibitors has occurred (Table 1) [Mahoney, 2015].

Agents that engage co-stimulatory pathways that lead to the proliferation and activation of T cells are also being evaluated in clinical trials. Essentially, optimal T-cell activation requires two

signaling events that prime these cells for activation [Sturgill ER, 2017]. Signal 1 occurs when the TCR binds antigenic peptides presented by the major histocompatibility complex on the surface of antigen presenting cells (APC). Signal 2 involves the engagement of cluster of differentiation (CD)28 on the T cell with B7-1(CD80) and B7-2(CD86) receptors on APCs; together these signals constitute the minimal co-stimulatory signals necessary for T cell activation. In addition, co-stimulatory signals via tumor necrosis factor receptors (TNFRs) are necessary to drive T cell differentiation/proliferation and potentiate the development of memory and effector subsets. TNFRs responsible for transducing the additional co-stimulatory signals needed for T cell activation include OX40 (CD134, tumor necrosis factor receptor superfamily [TNFRSF]4), glucocorticoid-induced TNFR (GITR, CD357, TNFRSF18), CD27 (TNFRSF7), and 4-1BB (CD137, TNFRSF9). The orchestration of these signaling events enables robust tumor killing activity by T cells *in vivo*. To exploit this important co-stimulatory cascade, agonist mAbs or ligands targeting TNFRs are in various stages of preclinical and clinical development for cancer (Table 1).

Table 1: Broad Categories of Drugs/Targets that Enhance T-cell Activation

Immune Checkpoint Antagonist/Inhibitors	Stimulatory Agonists
Anti CTLA-4	4-1BB (CD137, TNFRSF9)
Anti PD-1/ L1	OX40 (CD134, TNFRSF4)
Anti-LAG-3	GITR (CD357, TNFRSF18)
Anti-TIM-3	CD27 (TNFRSF7)
Anti-TIGIT	CD28

[Mahoney, 2015; Sturgill ER, 2017; Rataj, 2018]

Much excitement was generated when the first in class immune checkpoint inhibitors entered the clinic and elicited anti-tumor responses in patients with cancer [Postow, 2015]. Despite the initial success of PD-1/L1 and CTLA-4 inhibitors, clinical benefit as monotherapy occurs in a minority of patients (objectives responses in 10-45% with long term survival benefit in 20-30%). This has made the search for synergistic combinations or novel approaches an immediate priority. Along these lines, the first checkpoint-checkpoint combination of ipilimumab (CTLA-4 inhibitor) and nivolumab (PD-1 inhibitor) demonstrated improved response rates, progression free survival and overall survival compared to single agent therapy in late-stage melanoma albeit, with a high rate of severe toxicities [Larkin, 2015a; Larkin, 2015b; Boutros, 2016]. The use of other combination strategies pairing checkpoint inhibitors with stimulatory agonists are being explored in many ongoing clinical trials [Sturgill ER, 2017]. However, a critical issue is how best to combine and sequence these agents to elicit robust T cell responses against tumors.

Although combination immunotherapy can improve efficacy, developing novel treatment strategies remains a formidable task given the complexity of the human immune system and the potential for toxicity which may result from such interventions [Andrews, 2015]. Moreover, as only a proportion of patients benefit from these therapies, there is a need for systematic biomarker-driven approaches to identify patients most likely to respond to combination regimens targeting the immune system.

In an attempt to improve upon current paradigms, Shattuck Labs has developed a bifunctional fusion protein (FP) platform, capable of simultaneously blocking 'checkpoints' while activating TNFR co-stimulators. Shattuck's Agonist Redirected Checkpoint (ARC) platform adjoins the extracellular domain (ECD) of a select type 1 membrane protein to the ECD of a select type 2 membrane protein, via a central Fc domain. Using this approach, combination immunotherapy can be achieved by a single FP, having superior preclinical activity compared to the separate administration of two individual antibodies against identical targets.

1.2 Investigational Product, SL-279252

The investigational product (IP), SL-279252, is a first-in-class ARC FP consisting of the ECDs of human PD-1 and OX40L, linked by a central Fc domain (PD1-Fc-OX40L). The preclinical data supporting the translational study of SL-279252 in human subjects with cancer is described in detail in the Investigator's Brochure (IB) [SL2018IB001_01]. The mechanism of action, in vitro and in vivo pharmacology, toxicokinetics (TK), and the rationale for investigation are briefly summarized below.

1.2.1 Mechanism of Action

The mechanism of action of SL-279252 is designed to intercept one of the key immunosuppressive pathways within the TME: the PD-1 - PD-L1/PD-L2 axis. SL-279252 can bind to PD-L1 and PD-L2 expressed on tumor and antigen-presenting cells, and replace that inhibitory signal with OX40L, resulting in an incoming T cell experiencing co-stimulation via engagement through its OX40 receptor (Figure 1) instead of suppression through PD-1 interactions. Importantly, because the ECDs of PD-1 and OX40L are physically linked to one another and localized to the TME, tumor infiltrating T cells will receive co-stimulation at the same time they recognize a tumor antigen via the TCR.

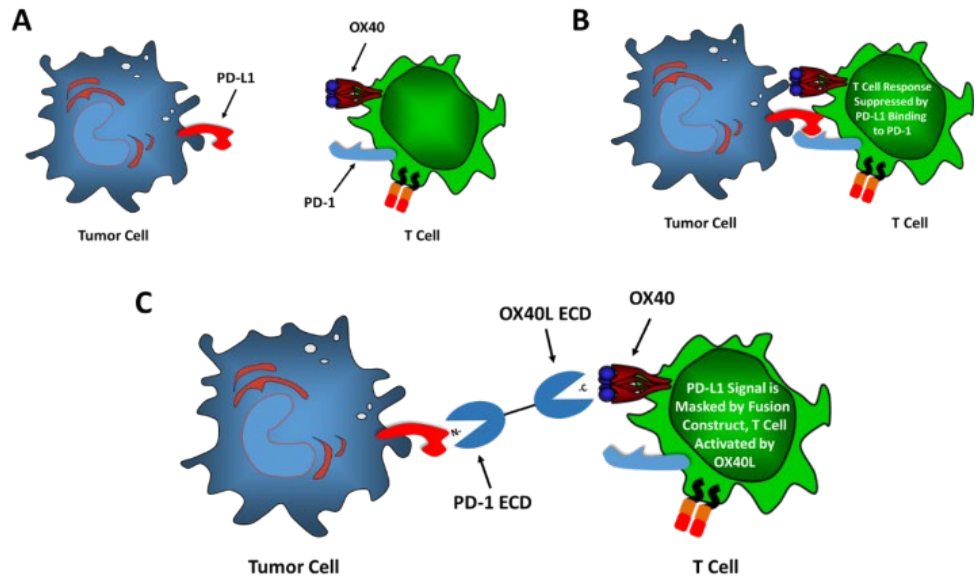


Figure 1: Mechanism of Action

(A) Tumor cell-expressed PD-L1 can bind to T cell-expressed PD-1 and (B) suppress activation. (C) SL-279252 can block this suppression while simultaneously providing T cell co-stimulation.

1.2.2 In Vitro Pharmacology

The PD-1 end of SL-279252, binds PD-L1 and PD-L2 with affinities of 2.08 and 1.76 nanomolar (nM), respectively, and the OX40L end binds OX40 with an affinity of 246 picomolar (pM). The PD1-Fc-OX40L ARC was also observed to have a considerably longer receptor off-rate constant (Kd) than control proteins (PD1-Fc and OX40L-Fc) when the dissociation from PD-L1 (18-fold longer), PD-L2 (13.4 fold longer) and OX40 (36-fold longer) was determined. The PD-1 domain efficiently outcompetes PD-L1 blocking antibodies for ligand binding, and the OX40L domain potently stimulates OX40-mediated nuclear factor kappa B signaling in a luciferase-based reporter assay. Furthermore, when activated human T cells were co-cultured with PD-L1 positive human tumor cells, SL-279252 enhanced proliferation of T cells and production of interleukin (IL)-2), interferon-gamma (IFNγ) and tumor necrosis factor alpha (TNF-α), which led to efficient killing of tumor cells.

1.2.3 In Vivo Pharmacology

The anti-tumor activity of the murine equivalent of SL-279252 (mPD1-Fc-OX40L) in established murine tumors was significantly superior to either PD-1 blocking, OX40 agonist, or combination antibody therapy. SL-279252 was shown to provide higher rates of tumor rejection and long-term immunity to tumor re-challenge than any of the antibody treatments in preclinical tumor models, including expansion of tumor antigen specific CD8 T cells. The SL-279252 drug product is a combination of trimers and hexamers resulting in highly potent signaling. Thus, all agonist functions of SL-279252 are independent of Fc receptor cross-linking. Collectively, preclinical data demonstrate a highly potent FP platform, providing checkpoint blockade and TNFRSF co-stimulation in a single molecule.

1.2.4 Toxicology

The cynomolgus macaque was selected for the toxicology studies due to the cross-reactivity of SL-279252 to the respective targets in this species. The anatomical, physiological, and biochemical similarities to humans facilitate extrapolation of observed pharmacokinetic (PK) properties to human.

Toxicology studies in non-human primates (NHP) (Table 2) were designed to evaluate the toxicity and identify the maximum tolerated dose (MTD) and TK of SL-279252 in cynomolgus monkeys following repeated weekly administrations (see the SL-279252 IB for further details). Repeat dose studies consisted of a dose range finding (DRF) study (2 Table 2A) and a Good Laboratory Practice (GLP) toxicity study (Table 2B). In both repeat dose studies, SL-279252 was administered intravenous (IV), once weekly, for up to 5 weeks. The doses evaluated in DRF study and GLP study were 3, 10, 50, and 100 milligrams per kilogram (mg/kg), and 10, 40, and 80 mg/kg, respectively. The GLP study included a vehicle control group. The GLP toxicity study also sought to evaluate the reversibility, progression or delayed appearance of any observed changes following a four week recovery period.

Table 2: Non-human Primate Studies

Table 2A Group Assignments [redacted]			
Group Number	Dose Level (mg/kg/dose)	Number of Animals	
		Male	Female
1	3	1	1
2	10	1	1
3	50	1	1
4	100	1	1
Table 2B Group Assignments [redacted]			
Group Number	Dose Level (mg/kg/dose)	Number of Animals	
		Male	Female
1	Vehicle	5	5
2	10	3	3
3	40	3	3
4	80	5	5

Across both studies, infusion-related reactions (IRRs) were the primary toxicity of concern. IRRs appeared to be dose- and time-dependent and were observed in GLP study [redacted] at 40 and 80 mg/kg doses in 4/6 and 9/10 animals, respectively. The IRR first occurred during or within 15 minutes (min) of the start of infusion (SOI) of the third dose of SL-279252. The manifestations of these reactions (decreased activity, flaccid limbs, pale gums/face, constricted pupils, closed eyelids, salivation, skin cold to touch, increased respiratory rate) were similar across animals and ranged in severity from mild to severe.

Deaths attributable to SL-279252 were noted in GLP study [redacted] at the 40 mg/kg and 80 mg/kg doses in 1/6 and 6/10 animals, respectively. Deaths occurred at the 5th dose in the 40 mg/kg cohort and at the 3rd and 4th dose in the 80 mg/kg cohort (Table 3). In DRF study [redacted], an IRR was observed after the 4th dose in 1 of 2 animals at the 100 mg/kg dose level. The onset and presentation were consistent with IRRs observed in GLP study [redacted].

Although severity and tissue distribution of histopathology findings were variable among affected animals, some consistency was noted in the type of findings and the organ/tissue distribution in the mid and higher dose group animals (≥40 mg/kg/dose) following repeat dose administration of SL-279252. These included vascular/sinusoidal leukocytosis, fibrin deposits mixed with predominant population of neutrophils, lymphocytes, and monocytes within vessels of lung, liver and/or kidney. Correlating laboratory findings were noted in affected animals. For the animals that died (Table 3), the cause of morbidity or euthanasia was due to leukocyte infiltration within the vascular lumina (vascular leukocytosis) as noted in the lungs, kidneys and liver sinusoids.

Table 3: Animal Deaths in GLP Study [redacted]

Dose (mg/kg)	Sex	Animal	Study Day of Death	Anti-Drug Antibody	Circumstances of Death	Target Dose Received (%)	Significant Pathology Findings
40	F	3501	29	Positive	Died after dosing	Day 1: ~100%. Day 8: ~100%. Day 15: ~100%. Day 22: ~100% Day 29: ~30%	Lung: vascular leukocytosis Liver: sinusoidal leukocytosis
80	M	4002	15	Positive	Died after dosing	Day 1: ~100% Day 8: ~100% Day 15: ~40%	Lung: hemorrhage and vascular leukocytosis
80	M	4004	15	Positive	Died after dosing	Day 1: ~100% Day 8: ~100% Day 15: ~40%	Lung: fibrin deposition and vascular leukocytosis
80	M	4005	15	Positive	Euthanized in extremis	Day 1: ~100% Day 8: ~100%. Day 15: ~40%	Liver: sinusoidal leukocytosis
80	F	4502	16	Positive	Euthanized in extremis	Day 1: ~100% Day 8: ~100%. Day 15: ~60%	Liver: sinusoidal leukocytosis Lung: hemorrhage, leukocytosis, fibrin deposition Kidney: hemorrhage, leukocytosis, fibrin deposition
80	M	4003	22	Positive	Died after dosing	Day 1: ~100%. Day 8: ~100%. Day 15: ~40%. Day 22: ~10%	Lung: fibrin deposition and vascular leukocytosis
80	F	4503	22	Positive	Euthanized in extremis	Day 1: ~100%. Day 8: ~100%. Day 15: ~10% Day 22 - ~30%	Liver: sinusoidal leukocytosis Lung: hemorrhage, leukocytosis, fibrin deposition Kidney: hemorrhage, leukocytosis, fibrin deposition

All animals tested screened negative for anti-drug antibodies (ADA) prior to dosing, and all animals in the vehicle group remained negative for ADA throughout the study. In contrast, all treated animals except for one screened positive for ADA prior to receiving the 3rd dose. All treated animals were positive for ADA prior to the 4th dose. For the two animals that demonstrated consumptive coagulopathy and were euthanized *in extremis* following the 3rd dose or 4th dose, the ADA titer was observed to decrease following dosing, which may have been due to immune complex formation. Overall, infusion reactions were associated with the formation of an ADA response by the time the 3rd dose was administered; however, the ADA titer did not correlate with the occurrence of an infusion reaction.

Cytokine levels were measured in both the [redacted] (Day 1, 29) and [redacted] (Day 1, 8, 15, 29) studies . There was evidence of an SL-279252-related increase in multiple cytokines, primarily interleukin-1 receptor antagonist, IL-10, IL-6 and monocyte chemoattractant protein-1 with lesser and more inconsistent increases in IL-18, IL-5, and macrophage inflammatory protein-

1b. Cytokine effects tended to peak at 2 hours postdose with resolution in most cases by 24 hours postdose, although occasional increased cytokine levels were seen at the 80 mg/kg/dose at one or more predose intervals (Days 8, 15, or 29). The magnitude of cytokine increases tended to follow a dose response, and often became more pronounced following the 3rd dose at which point all but one animal had developed ADA. No discernable effects on IFN-γ, IL-2, IL-4, IL-17-α, or TNF-α were identified in any group. In general, the profile of cytokines elevated is consistent with a T helper 2-type immune response. This profile could be consistent with OX40 activation in CD4+ T cells but interpretation is confounded by the presence of ADA.

Complement activation was also measured in both the [redacted] (Day 22, 29) and [redacted] study (Day 1, 8, 15, 29). Complement analysis demonstrated evidence of dose-related and progressive SL-279252 related complement activation at all dose levels as indicated by increases in split products Bb, C3a, and/or SC5b-9. These effects tended to peak at 2 hours post-dose with resolution in most cases by 24 hours post-dose. The magnitude of the effects tended to follow a dose response. Effects were observed following the first dose in all animals, with vehicle and 10 mg/kg dose groups showing mild elevation, while higher elevations were observed in the 40 mg/kg and 80 mg/kg dose groups. The magnitude of increase among complement endpoints tended to become more pronounced following the 3rd dose, with the effect also noted at the 10 mg/kg dose level and persisting through the 24-hour post-dose interval.

The bioanalytical assay measured only free, unbound SL-279525 and the TK results demonstrated targeted-mediated drug disposition (TMDD) following a single dose as there was a decrease in clearance (CL) and volume of distribution (Vz) with an increase in dose from 3 to 100 mg/kg. The apparent TMDD observed following the first dose was likely due to binding of SL-279252 to targeted receptors on the peripheral blood lymphocytes. The serum terminal phase half-life (t½) ranged from approximately 12 to 25 hours over doses ranging from 3 to 100 mg/kg for the combined DRF and GLP toxicology study. Interestingly, SL-279252 was detected on peripheral blood lymphocytes by flow cytometry up to 7 days post-infusion and by Day 15 was accompanied by expansion of OX40 positive lymphocytes and a consistent serum cytokine signature. Based on the evidence of TMDD likely related to binding to receptors localized on peripheral blood lymphocytes, CL of SL-279252 may be affected by changes to lymphocyte count and/or receptor density. The TK profiles observed on Day 29 following weekly administration of SL-279252 were atypical with rapid clearance of free SL-279252. By Day 29, all animals in the DRF and GLP toxicity study tested positive for ADA which likely explains the rapid clearance observed following administration on Day 29.

Taken together the findings from the DRF [redacted] and GLP [redacted] studies were suggestive of expected target-mediated pharmacology as well as immunogenicity related effects which led to dose-dependent toxicity. The immune effects were considered to be multifactorial in etiology with potential contributions from cytokine increase, complement binding and ADA-mediated effects. Collectively, the effects at 40 and 80 mg/kg/dose were considered adverse and the effects at 10 mg/kg/dose were not considered adverse. The highest non-severely toxic dose (HNSTD) was determined to be 10 mg/kg.

1.3 Rationale

The preclinical data package provided in the IB [SL2018IB001_01] demonstrates that the tethering of these two signals using an ARC provides a mechanistic advantage over the separate administration of two antibodies that have different PK properties, distribute separately, and may compete for Fc receptor binding. We hypothesize that co-localization and co-stimulation is critical for combination immunotherapy and will result in superior clinical activity in comparison to the separate administration of two individual antibodies. In addition, SL-279252 has a strong specificity advantage over mAbs targeting a specific co-stimulatory ligand (i.e., PD-L1 inhibitors like atezolizumab, avelumab, and durvalumab), when multiple ligands exist for a given target and can all (at least partially) contribute to the overall immunosuppressive environment. For example, blocking only PD-L1 does not preclude an incoming T cell from becoming suppressed when its membrane bound PD-1 interacts with tumor expressed PD-L2. SL-279252 binds to PD-L2 with similar affinity as it does to PD-L1 and is able to occupy/block both ligand binding sites.

SL-279252 also overcomes several major functional limitations seen with existing bifunctional technologies (i.e., bispecific antibodies or linked single-chain variable fragment [scFv] molecules). The active unit of SL-279252 exists as a glycosylated multimer, thereby retaining high target avidity, and inducing OX40 receptor clustering and active signaling. The TNF superfamily receptors (i.e., OX40, GITR, 4-1BB) require clustering on a cell membrane and coordinated binding of multiple receptors for signal activation. With bispecific antibodies or linked scFv molecules, one of the two target binding domains is replaced to bind a second molecule thus resulting in a loss of target avidity. The monovalent binding interaction with each of these two targets is incapable of activating receptors that require clustering on a cell membrane. For this reason, there is not a current example of a bispecific antibody or linked scFv that is able to simultaneously block a checkpoint ligand while stimulating a TNF costimulatory receptor.

This first-in-human Phase 1 study will evaluate the safety, tolerability, PK, anti-tumor and pharmacodynamic effects of SL-279252 to identify the dose and schedule i.e., recommended Phase 2 dose (RP2D) for future development. The trial will enroll patients with tumor types that have demonstrated benefit from anti-PD1/L1 inhibitor therapy i.e., melanoma, non-small cell lung cancer (NSCLC), urothelial cancer, head and neck squamous cell carcinoma (HNSCC), squamous cell cervical cancer, gastric or gastro-esophageal junction (GEJ) adenocarcinoma, squamous cell carcinoma of the anal canal (SCCA), squamous cell carcinoma of the skin (Skin-SCC), renal cell cancer (RCC), Hodgkin's lymphoma (HL), and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding central nervous system (CNS) malignancies. Given that SL-279252 likely requires binding of PD-L1 to mediate activity within the tumor, the study was amended to require eligible subjects to have tumors with PD-L1 expression ≥1% by tumor proportion score (TPS) or combined proportion score (CPS) at baseline.

Potential risks to subjects are addressed by safety guidelines and vigilant monitoring of participants as outlined in the protocol. Potential safety concerns are based on preclinical safety toxicology findings in cynomolgus monkeys dosed with SL-279252 and other in vivo or in vitro studies of SL-279252 summarized in the IB, as well as established clinical management guidelines developed for immune checkpoint therapy inhibitors.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

SL-279252 is a pharmacologically active molecule [SL2018IB001_01]. The risks (evaluation of safety and tolerability) and potential benefits (evaluation of anti-tumor activity) of SL-279252 in humans will be assessed for the first time in this Phase 1 clinical trial. In the absence of data in humans, an assessment of potential safety risks is based on (1) the results of nonclinical studies with SL-279252 (e.g., NHP studies); and (2) the immune-related adverse event (irAE) profile of other immune checkpoint inhibitors and costimulatory molecules.

Based on a thorough review of the totality of the NHP data (including laboratory studies, cytokine and complement data, TK and immunogenicity studies, anatomical pathology), the underlying etiology of the SL-279252-related effects is most likely due to a combination of both the pharmacologic activity of the molecule and to immunologic reactions to SL-279252 administration. The following are potential contributory factors to these reactions: (1) high levels of cytokine release; (2) increase in pre-dose lymphocytes; (3) development of ADA; and/or (4) complement activation.

Implications for the first-in-human clinical trial [SL2018IB001_01]:

1) The data indicate a potential risk for cytokine release syndrome (CRS) in humans. The IRRs that were noted in the NHP studies were potentially cytokine-mediated as they demonstrated dose- and time-dependence. In contrast, antibody-mediated type 1 or type 3 hypersensitivity reactions (HSRs) would not be expected to demonstrate dose-dependence. Furthermore, CRS is to be expected given the mechanism of action of SL-279252. The steps taken to minimize the risks include: low starting dose, decreased dose frequency in comparison to the dosing schedule for the NHP studies for the first schedule to be evaluated (i.e., Schedule 1), administration in an outpatient oncology clinic or inpatient setting, management guidelines (e.g., rescue treatments, prophylaxis), extended monitoring in a hospital setting and/or hospital admission when indicated. The steps taken to minimize the risks are outlined in the Toxicity Management Guidelines section of the protocol (Section 3.5).

2) Immunogenicity Risk: SL-279252 is considered to have a low risk of immunogenicity in humans. To evaluate the risk of immunogenicity in humans, the following 2 in vitro studies were performed: (1) Antitope/Abzena in silico analysis showed that the SL-279252 construct did not contain any identifiable T cell epitopes; and (2) EpiScreen™ time course T cell assay assessed the probability for SL-279252 to induce CD4+ T cell responses. No proliferation or cytokine release was observed in this assay with peripheral blood mononuclear cells (PBMCs) from 50 healthy donors. Subjects in the clinical trial will, nevertheless, be monitored starting at baseline and serially for ADA. In the event of a positive ADA response, antibody titer will be measured, and antibody isotype will be characterized. A guideline for monitoring and management of HSRs is included in the protocol (Section 3.5.1).

3) Toxicity secondary to complement activation: Complement activation secondary to treatment with SL-279252 could potentially result in toxicity. In the NHP studies, SL-279252 caused complement activation in vivo, as measured by CH50, C3a, Bb and SC5b9 assays. The cynomolgus monkey is a sensitive species for complement activation [Shen, 2014]. Thus, in

vitro assays were performed to determine whether SL-279252 directly activated human and/or cynomolgus complement proteins. The magnitude of complement activation observed in vitro appears to be increased in cynomolgus monkey serum as compared to human serum. It was noted that SL-279252 activated human and cynomolgus complement proteins in vitro at concentrations above 15.3 µg/mL. Based on toxicokinetic simulations, less than 1% of subjects will have a serum concentration of SL-279252 exceeding 15.3 microgram/milliliter (µg/mL) at human doses below 0.3 mg/kg. Patients in the clinical trial will be monitored for complement activation at all dose levels.

As with other checkpoint inhibitors and costimulatory molecules, irAEs resulting from a breakdown of self-tolerance are anticipated with SL-279252. As experience using these therapies has grown, the list of toxicities has increased, and the types of AEs observed span essentially every organ class. Extensive knowledge in managing these toxicities has developed over the years and led to the publication of consensus guidelines in peer reviewed journals [Haanen, 2017; Puzanov, 2017; Brahmer, 2018]. Similarly, robust management guidelines are available for managing CRS in the context of treatment with adoptive T-cell therapies, bispecific antibodies, and agonist antibodies. Moreover, clinical trial sites familiar with these therapeutic agents have developed institutional guidelines to ensure effective management of these toxicities. Monitoring and management of irAE follow these consensus guidelines in this first in human study.

In summary, this Phase 1 study has taken the following precautions to minimize the potential for adverse outcome: (1) the study is being conducted at centers that have extensive experience with this class of agents and the management of associated toxicities; (2) the starting dose of SL-279252 is estimated based on minimum anticipated biological effect level (MABEL) and is 100,000x lower than the HNSTD observed in the NHP studies (Section 3.2.3). Therefore, the starting dose is expected to be lower than doses associated with adverse events (AEs) in humans; (3) staggered enrollment between dose cohorts and within cohorts allows for the monitoring of acute toxicities in one subject before treating another; (4) administration of SL-279252 in an outpatient oncology treatment center/hospital allows for close monitoring of subjects for AEs and for timely action; (5) guidelines for management of AEs based on established guidelines [Haanen, 2017; Puzanov, 2017; Rosello, 2017; Brahmer, 2018; Porter, 2018] are provided in the clinical trial protocol (Section 3.5); (6) a Safety Monitoring Committee (SMC) will meet monthly and on an ad hoc basis to review emerging toxicities, and assess the impact of these toxicities on study conduct.

1.4.2 Potential Benefits

The clinical benefits of SL-279252 are unknown: no clinical trials in human subjects have been conducted to date. SL-279252 targets both the PD-1/L1 and the OX40/OX40L axes. Mabs targeting each of these axes have been extensively evaluated in clinical trials [Marin-Acevedo, 2018].

PD-1/L1 inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab) have demonstrated a favorable benefit:risk profile in clinical trials and gained regulatory approval in an expanding array of indications. HL harbors genetic alterations in the chromosome 9p24.1 amplicon, resulting in overexpression of the PD-1 ligands, PD-L1 and PD-L2 [Roemer, 2016]. This makes HL unique among all tumors. The overall response rates in patients with

relapsed/refractory HL were 87% and 65%, with nivolumab and pembrolizumab, respectively [Ansell, 2015; Armand, 2016]. In other tumor types depending on the indication, clinical responses have been less impressive (reported in 10-45% of patients) [Larkin, 2015b; Carbone, 2017; Grywalska, 2018]. The most mature survival outcome results for checkpoint inhibitors are in advanced melanoma. A pooled analysis of 12 clinical trials of ipilimumab in patients with advanced melanoma with follow-up to 10 years revealed a plateau at 21% in the survival curve beginning around year 3 [Schadendorf, 2015]. In a survival follow-up of patients who received nivolumab in advanced melanoma, the 60-month overall survival rate was 34% with a plateau occurring at approximately (~) 48 months [Hodi, 2016]. In a quest to improve on such results, PD-1 inhibitors have been combined with other agents including checkpoint inhibitors, costimulatory agents, vaccines, chemotherapeutic agents, targeted therapies and radiation. Along these lines, the first checkpoint-checkpoint combination of ipilimumab (CTLA-4 inhibitor) and nivolumab (PD-1 inhibitor) was approved for late-stage melanoma based on a significant improvement in progression free survival compared to ipilimumab [Larkin, 2015a].

Despite promising preclinical results of anti-tumor activity with OX40 agonists, early clinical trials of these agents as monotherapy have been underwhelming. Combination immunotherapy trials with PD-1 inhibitors and anti-OX40 antibodies are ongoing but results are pending. However, the data from the preclinical studies for this combination has been conflicting. In vivo experiments in mice have demonstrated that simultaneous addition of anti–PD-1 to anti-OX40 antibodies negates the antitumor effects of the anti-OX40 antibody [Messenheimer, 2017; Shrimali, 2017]. In contrast, sequential combination of anti-OX40 antibody followed by anti-PD-1 antibody (but not the reverse order) resulted in significant increases in therapeutic efficacy [Messenheimer, 2017]. These results suggest that in some cases the sequencing of agents must be carefully considered due to competition for Fc receptor binding [Gao, 2017]. The synchronized blockade of immune suppression and costimulation of T cells is more difficult to achieve if separate antibodies are administered, as opposed to a single agent designed to engage both targets simultaneously [SL2018IB001_01]. This hurdle could be overcome by an immunotherapeutic such as SL-279252. The ECDs of PD-1 and OX40L are physically linked to one another and localized to the TME. Tumor infiltrating T cells will receive costimulation at the same time that they recognize a tumor antigen via the T cell receptor.

This first in human, Phase 1 trial will assess the safety, tolerability, PK, pharmacodynamics and anti-tumor activity of SL-279252 in patients with tumor types that have been documented to respond to anti-PD1/L1 therapy. All patients enrolled in this trial are required to have received or been intolerant to standard of care therapies. The majority of subjects will also have received PD1/L1 and/or CTLA-4 inhibitors and progressed.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Table 4: Study Objectives and Outcome Measures

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);

Objective	Outcome Measure
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

Objective	Outcome Measure
Exploratory Objectives	
Dose Escalation and Dose Expansion To explore additional measures of anti-tumor activity of SL-279252	• Duration of response (DOR): time between first response (iCR or iPR, whichever is recorded first) and date of disease progression) • Time to response (TTR): time from the start of treatment with SL-279252 to the first objective tumor response (iCR or iPR, whichever is recorded first) • Progression free survival: time from first dose of SL-279252 to progression or death, whichever comes first • Overall survival: time from first dose of SL-279252 to death
Dose Escalation and Dose Expansion : To explore relationship between PK/pharmacodynamics and the relationship between PK and clinical activity including tumor growth kinetics	PK/pharmacodynamics and clinical activity outcomes as described above

3. STUDY DESIGN

3.1 Description of Study Design

This is a Phase 1 first in human, open label, multi-center, 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. The tumor types selected have been reported in the literature to be responsive to PD-1/L1 inhibitors. 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. A subset of one or more selected tumor type(s) from the list of eligible histologies may be identified for enrollment in dose escalation. 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.

The study design consists of Dose Escalation (Section 3.2) and Dose Expansion Cohorts (Section 3.3). In the dose escalation phase of the study, subjects will be enrolled into sequential dose levels (DL) as outlined in Section 3.2.4 and Table 5. Enrollment into a DL cohort will follow the Keyboard Design outlined in the Appendix Section 16.3 [Yan, 2017].

During dose escalation, two possible schedules (Schedule 1 and Schedule 2) for administration of SL-279252 may be explored as outlined in Section 3.2.4. Schedule 1 will be evaluated first. A transition to Schedule 2 may be implemented for reasons outlined in Section 3.2.7. If Schedule 2

is opened for enrollment, then enrollment on Schedule 1 will be halted. 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 support less frequent dosing of SL-279252.

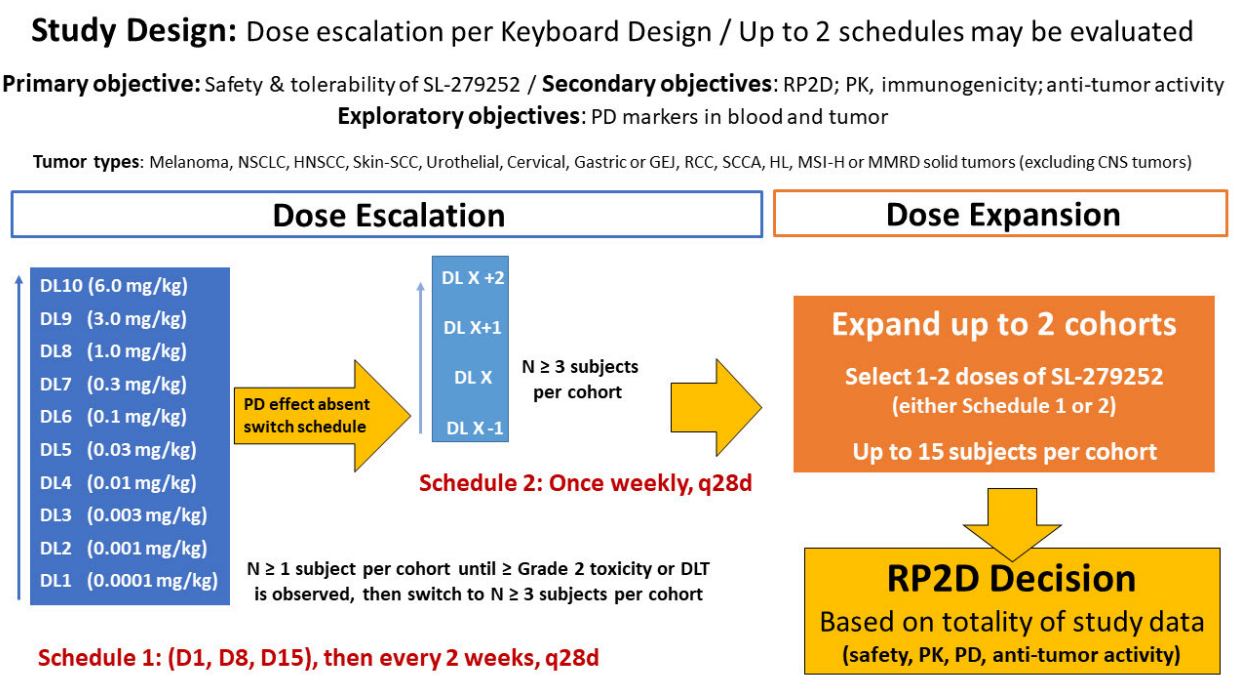
Pharmacodynamic Cohorts in Dose Escalation: The Sponsor, in consultation with the SMC, may elect to open a pharmacodynamic cohort in order to obtain additional pharmacodynamic data from a total of approximately 6 additional subjects at one or more dose levels that have previously completed evaluation 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. As a result, the maximum planned sample size estimate in dose escalation may increase by approximately 6 subjects and the overall total planned sample size estimates would increase accordingly. Subjects in the pharmacodynamic cohort will be followed per the Dose Escalation Schedule of Assessment (SOA) tables provided in Sections 6.1 (schedule 1) and 6.2 (schedule 2).

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. **NOTE:** Only one schedule will be evaluated in the expansion phase. The primary objective of the expansion phase is to further refine the safety and tolerability of SL-279252. The expansion cohorts will also provide additional pharmacodynamic data and a preliminary estimate of anti-tumor activity. At the end of dose escalation and dose expansion, safety, PK, anti-tumor activity, and pharmacodynamic data will be reviewed to identify a RP2D (Section 3.3.2).

3.1.1 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 (see Section 3.3 for details). 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. See Sections 9.2.1 and 9.2.2 for more details.

3.1.2 Study Schema



Safety evaluation of SL-279252 will begin on Schedule 1. Dose escalation will proceed as described in Section 3.2.4 and Table 5. Initially, cohort size may be limited to 1 subject for enrollment until ≥ Grade 2 toxicity or DLT (see Section 3.2.5 for criteria to expand single subject cohort size and Section 3.2.6 for DLT definitions) is observed or DL 6 is reached; any of these scenarios trigger enrollment of ≥ 3 subjects in dose cohorts from that point forward. Enrollment into a DL will proceed based on the Keyboard Design outlined in the Appendix Section 16.3. Schedule 2 will be tested if investigation of a more frequent dosing schedule is considered necessary (Section 3.2.7). The starting dose on Schedule 2 will be at least 1 DL below the current safe Schedule 1 DL defined by the Keyboard design (denoted as DL X-1 in the schema above). An MTD or MAD may be identified on either Schedule 1 or Schedule 2. Up to 2 doses may be selected for further evaluation in dose expansion cohorts and up to 15 subjects may enroll per cohort. Only dose levels that have been cleared for safety (permitted to escalate per the Keyboard Design rules) with a minimum of 6 subjects treated at that dose level will be expanded. The Dose Expansion cohorts may be opened to enroll subjects in parallel with the Dose Escalation cohorts. Fresh tumor biopsies (obtained prior to C1D1, during C1D16 to C1D23, and at progression) are requested of subjects in Dose Escalation or Expansion cohorts who have tumor accessible to biopsy. In addition, blood will be obtained for serial assessment of PK and relevant biomarkers during dose escalation and dose expansion. A pharmacodynamic cohort may also be explored during dose escalation as described in Section 3.1. A RP2D will be selected for further evaluation at the end of the study based on the totality of the data.

Abbreviations for Schema: D and d = Day; DL = dose level; MAD = maximum administered dose; MTD = maximum tolerated dose; PD = pharmacodynamic; PK = pharmacokinetics; q = every; RP2D = recommended phase 2 dose

3.2 Dose Escalation

3.2.1 Description

Dose escalation will proceed as described below. Enrollment will be based on the Keyboard Design outlined in the Appendix Section 16.3 [Yan, 2017]. During dose escalation, two possible

schedules for administration of SL-279252 may be explored. The first schedule (Schedule 1) will determine the safety of 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. The second schedule (Schedule 2) will explore the safety of weekly dosing of SL-279252 on days 1, 8, 15 and 22 of each 28-day cycle. The DLT assessment period will end 7 days after the last dose administered in the first cycle. Therefore, DLTs will be assessed over 21 days for Schedule 1 and over 28 days for Schedule 2. DLTs are defined in Section 3.2.6.

Enrollment on Schedule 2 may be instituted if safety and pharmacodynamic data support exploration of more frequent dosing based on defined inadequate evidence of pharmacodynamic activity on Schedule 1 (see Section 3.2.7). The starting dose on Schedule 2 will be at least 1 DL below the current safe Schedule 1 DL defined by the Keyboard design. Doses beyond the maximum dose stated in the protocol may be explored if the MTD has not been reached. In summary, an MTD or MAD may be determined on Schedule 1 or Schedule 2 depending on how the study evolves. Alternatively, a less intensive dosing schedule may be instituted if safety and pharmacodynamic data on Schedule 1 support less frequent dosing of SL-279252 (e.g., one dose given every two weeks or every three weeks or every four weeks).

Blood will be collected prior to, during, and following SL-279252 administration for serial assessment of PK (Section 6.7.1) and relevant biomarkers (e.g., cytokines, complement, receptor occupancy, etc.) during dose escalation (Section 6.9.1). Tumor tissue (archival tissue and fresh tumor biopsies predose, on-treatment and at progression) will be requested of subjects as described in Section 6.9.2.

3.2.2 Intrasubject Dose Escalation

For subjects enrolled in Dose Escalation cohorts, intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject completed at least 2 cycles at the originally assigned dose, has tolerated treatment well, and did not experience Grade 3 or higher toxicity. A subject's dose may be increased to that of the current DL that has been evaluated for safety and has not exceeded the MTD. Approval for intra-subject dose escalation must be obtained from the Sponsor Medical Monitor. Dose-escalation decisions will be documented on a Dose Escalation/De-escalation Decision Form (see the Study Reference Manual; SRM).

3.2.3 Justification for Starting Dose

The starting dose of 0.0001 mg/kg SL-279252 for this first in human study was derived using available nonclinical pharmacology, toxicology, PK and pharmacodynamic data from NHP studies in the cynomolgus species. The starting dose was selected based on MABEL principles.

In cynomolgus monkeys administered IV doses of 0.03 and 0.3 mg/kg over 30 minutes (n=2 for each DL) resulted in median Cmax values of 564 and 7464 nanogram (ng)/mL, respectively, which are approximately 738- and 56-fold below the Cmax observed in monkeys for the HNSTD dose of 10 mg/kg (416,000 ng/mL). Assuming linear kinetics from the 0.03 mg/kg dose in cynomolgus monkeys (Cmax 564 ng/mL and $AUC_{0\text{-infinity [inf]}}$ 304 ng*h/mL), a 0.0001 mg/kg dose of SL-279252 would achieve an estimated Cmax of 1.88 and $AUC_{0\text{-inf}}$ of 1.01 ng*h/mL which is

approximately 200,000- and 700,000-fold lower than the Cmax and $AUC_{0\text{-}inf}$ observed for the HNSTD dose of 10 mg/kg (Cmax 416,000 ng/mL; $AUC_{0\text{-}inf}$ 726,000 ng*h/mL).

However, because non-linear kinetics were observed for SL-279252 following single dose IV infusion in cynomolgus monkeys, a PK model was developed to capture the PK in monkeys adequately and to facilitate human exposure predictions. The PK model for serum SL-279252 concentrations following a single dose was developed using a two-compartment model with Michaelis-Menten clearance and allometric scaling by body weight on clearance and volume parameters. After accounting for body weight, there were no other important covariates in the model. The model tended to over-predict Cmax for the lowest doses (0.03 and 0.3 mg/kg) in monkeys by 1.2- to 2.1-fold, thus, the model was deemed a conservative model for simulating human exposure.

Simulated human serum SL-279252 concentrations suggest that a starting dose of 0.0001 mg/kg results in median (95% confidence interval [CI]) Cmax of 3.73 (2.83, 4.92) ng/mL and is 111,500-fold lower than the median Cmax following administration of the HNSTD dose (416,000 ng/mL). Simulated concentrations for the 0.0001 mg/kg dose are almost 10-fold below the Staphylococcal Enterotoxin B (SEB) Activity Assay half maximal effective concentration (EC50; geometric mean and 95% CI of 34.0 [21.3 – 54.4] ng/mL) MABEL. While simulations of a 0.0001 mg/kg dose result in concentrations that are comparable to the SEB Assay EC20 (5.3 [2.69, 10.4] ng/mL), the SEB Assay is known to be a sensitive assay and given the in vivo data, it is likely a single dose of 0.0001 mg/kg will result in minimal to no biologic activity. Simulation of SL-279252 concentrations following multiple doses were not possible with the available data.

Justification for Schedule: A weekly dosing schedule for 5 consecutive weeks was implemented in the NHP studies. Toxicity was dose-dependent (only at the higher doses) and occurred at the third and subsequent doses. In the clinical trial, the initial dosing schedule (Schedule 1) incorporates administration of SL-279252 on Day 1, 8, 15, and then every 2 weeks thereafter. The Day 8 dose was retained as no toxicity was observed at this time point, minimal pharmacodynamic effects were noted, and this dose may have contributed to the pharmacodynamic effect on day 15. In NHPs, multiple factors may have contributed to the onset of reactions at Day 15 including ADA, complement activation, increase in lymphocytes and cytokine elevations. It is unknown if these contributing factors would be observed in humans at the doses studied. Therefore, dosing on Day 1, 8, 15 was considered acceptable. The 2-week treatment free interval beyond Day 15 may allow for pharmacodynamic effects to subside between subsequent doses and to mitigate toxicity. A less intensive dosing schedule may be instituted if safety and pharmacodynamic data on Schedule 1 support less frequent dosing of SL-279252 (e.g., one dose given every two weeks or every 3 weeks or every 4 weeks).

3.2.4 Starting Dose and Dose Escalation Plan

Enrollment of subjects at each DL proceeds based on the Keyboard design outlined in the Appendix Section 16.3. Dose escalation will begin on Schedule 1 at the starting dose of 0.0001 mg/kg as outlined in Table 5 below; intermediate DLs not shown may be explored based on emerging data (e.g., safety). As it is likely that the dose of 0.0001 mg/kg will result in minimal to no biologic activity, escalations for the first two DLs will proceed in log increments. Beyond DL2,

escalations will not exceed half-log increments. Doses beyond the maximum dose stated in the protocol may be explored if the MTD has not been reached. An MTD or MAD may be determined on Schedule 1 or Schedule 2 and up to 10 or more dose levels may be explored if safety allows.

Table 5: SL-279252 Dose Escalation Plan

Dose Level	Dose of SL-279252 (mg/kg)[a,b,c,d]	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 (See Sections 5.2.3 and 5.4 for details)

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, and as outlined in Section 16.3.1, 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 Sections 3.2.5 and 3.2.6 for definitions) or DL 6 is reached; any of these scenarios will trigger enrollment of ≥ 3 subjects in 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 SMC. The incidence of DLT will be assessed over a period of 21 days during the first cycle of therapy (DLTs are defined in Section 3.2.6) on Schedule 1.

Evaluation of Schedule 2: If safety and pharmacodynamic data from Schedule 1 (see Section 3.2.7 for criteria needed to transition to Schedule 2) support exploration of more frequent dosing, then cohort enrollment on Schedule 2 will be instituted in lieu of Schedule 1. During dosing on Schedule 2, SL-279252 will be administered once weekly (D1, D8, D15, and D22) every 28 days. 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 5. 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, although this mandate may change based on emerging safety data. The incidence of DLT will be assessed over a period of 28 days during the first cycle of therapy (DLTs are defined in Section 3.2.6) on 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. For example, SL-279252 may be administered once every two weeks in every cycle including the first cycle or once every 21 or 28 days. The starting dose on this less intensive schedule would be instituted at the current Schedule 1 dose level defined by the Keyboard design or a lower dose level based on emerging safety data.

3.2.5 Criteria for Expanding a Single Subject Cohort in Schedule 1

Dose escalation on Schedule 1 allows enrollment of a single subject (minimum of one subject per DL) into dose levels 1 to 5 unless a Grade ≥ 2 toxicity or DLT (Section 3.2.6) is observed over the 21-day DLT assessment period with the exceptions listed below. A qualifying event of Grade ≥ 2 toxicity or DLT will trigger a switch to enrollment of ≥ 3 subjects for DLT assessment in that specific dose level and each DL thereafter.

Toxicity exceptions that will not trigger a switch to enrollment of ≥ 3 subjects:

- Grade 2 fatigue
- Grade 2 nausea and vomiting controllable with anti-emetics within 72 hours
- Vitiligo and alopecia of any Grade
- Grade 2 IRR that can be managed with premedication and/or change in infusion duration
- Grade 2 hematologic abnormalities not associated with clinical signs/symptoms
- Grade 2 electrolyte abnormalities that are not associated with clinical signs/symptoms
- Grade 2 amylase and lipase without evidence of clinical symptoms of pancreatitis
- Toxicities related to disease progression or intercurrent illness, inflammatory reactions related to local tumor response such as severe pain

3.2.6 Definition of Dose-Limiting Toxicity

DLTs are defined in the bulleted points below. Toxicities will be graded as per NCI CTCAE v5. The determinate period for DLT is the first 21 days or 28 days of treatment on Schedule 1 or Schedule 2, respectively. However, there is provision in the criteria below for toxicities that occur beyond this period to be considered in the definition of a DLT and the RP2D. **Note**: Toxicities clearly related to disease progression or intercurrent illness are not considered DLTs. Inflammatory reactions attributable to local anti-tumor responses (e.g., severe pain) are not considered DLTs.

- Any Grade 4 irAE
- Elevations in liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and/or total bilirubin:
    - In subjects who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN); AST or ALT elevation of >8 x ULN **or** total bilirubin > 5 x ULN
    - In subjects who enroll with AST/ALT/total bilirubin > ULN; AST or ALT elevation of >8 x baseline **or** total bilirubin > 5 x baseline
    - Evidence of Hy's Law (AST or ALT > 3 x ULN [or baseline*] with concurrent increase in total bilirubin > 2 x ULN [or baseline*] without evidence of cholestasis or alternative explanation such as disease progression or viral hepatitis; *ULN or baseline dependent on value at enrollment as described above.
- Any Grade 3 irAE that requires permanent discontinuation of SL-279252
- Any other Grade 3 irAE with the following exceptions:
    - Grade 3 skin toxicity that downgrades to Grade 2 or less within 7 days with optimal supportive care
    - Grade 3 hypothyroidism, hyperthyroidism, or hyperglycemia that can be managed with treatment
    - Grade 3 diarrhea with no evidence of colitis that resolves within 72 hours with appropriate clinical management
- The following Grade 2 irAEs:
    - Grade 2 ocular toxicity requiring systemic steroids
    - Grade 2 cardiotoxicity that requires permanent discontinuation of SL-279252
    - Grade 2 Guillain-Barre Syndrome
- Any Grade 3 or greater non-irAE **except** for those listed below:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 or 4 neutropenia not associated with fever that improves to Grade 2 within 7 days.
    - Grade 3 or 4 lymphopenia
    - Grade 3 thrombocytopenia not associated with clinically significant bleeding and does not require medical intervention
    - Grade 3 electrolyte abnormalities that are not associated with clinical signs/symptoms and are reversed with appropriate medical intervention

- Grade 3 or 4 amylase and/or lipase abnormalities that are not associated with clinical signs/symptoms or finding on imaging consistent with pancreatitis
- Grade 3 vomiting and/or Grade 3 nausea that resolves within 72 hours with appropriate clinical management

- Other toxicities may be considered a DLT as determined by the investigator in conjunction with the SMC.

A Grade ≥ 3 AE that occurs beyond the DLT period (21 days for schedule 1 or 28 days for schedule 2) or Grade 2 events that require continuous interruption of SL-279252 for more than 6 weeks or toxicities that result in subjects not receiving at least 66% of the scheduled dose during the DLT assessment period may be taken into consideration when assessing the totality of the data in determining evaluability for DLT and the RP2D.

3.2.7 Criteria for Decision to Transition from Schedule 1 to 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 an alternative dosing schedule (Schedule 2) will be explored in lieu of Schedule 1. During dose escalation subjects will be monitored for pharmacodynamic effects pre- and post-dose. Dynamic changes that are anticipated following administration of pharmacologically active doses of SL-279252 include:

- Evidence of increasing target density on PBMCs following repeated dosing
- Increase in lymphocyte count
- Increase in cytokines
- Appearance of activation markers (e.g., Human Leukocyte Antigen D Related, CD25, etc.) on the surface of CD4 lymphocytes in the peripheral blood

The anticipated timing of pharmacodynamic effects based on NHP studies is at cycle 1, day 15 (C1D15) and beyond, although these effects may be observed as early as C1D1 and C1D8.

3.3 Dose Expansion

3.3.1 Description

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 primary objective for the Dose Expansion Cohorts is to further refine the safety and tolerability of SL-279252. Safety will be carefully monitored, and sequential boundaries will be used to monitor for IRRs and discontinuation of SL-279252 due to toxicity based on Pocock stopping rules [Ivanova, 2005] as outlined in Section 9.2.2. The expansion cohorts could potentially begin enrollment prior to the end of dose escalation. Only dose levels that have been cleared for safety (permitted to escalate per the Keyboard Design rules) with a minimum of 6 subjects treated at that dose level will be expanded. Up to 15 subjects will be evaluated in each

Expansion Cohort at a selected dose. 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.

Secondary objectives for the dose expansion cohorts include a preliminary estimate of anti-tumor activity as measured by ORR and CBR. In addition, exploratory pharmacodynamic objectives will be further examined in the Dose Expansion Cohorts. Blood will be collected prior to and following SL-279252 administration for assessment of PK (sparse sampling; Section 6.7.2) and relevant biomarkers (e.g., cytokines, complement, immunophenotyping, etc.) during dose expansion (Section 6.9.1). Tumor tissue (archival tissue and fresh tumor biopsies predose, on-treatment and at progression) will be requested of subjects in Expansion Cohorts as described in Section 6.9.2. Cell-free or circulating-free tumor nucleic acid (cfNA; see Section 6.9.1.4) and archival tumor tissue (Section 6.9.2.2) will be obtained for retrospective assessment of tumor mutational burden (TMB).

3.3.2 Selection of Recommended Phase 2 Dose and Schedule for SL-279252

If an MTD is not observed, the MAD would then be the highest dose administered as specified in the protocol. Selection of the dose and schedule for further study will therefore be based upon safety, tolerability, PK, anti-tumor activity, and pharmacodynamic markers consistent with the mechanism of action of SL-279252. Exploratory PK/pharmacodynamic modeling will be performed. Based on the totality of the data, from the Dose Escalation and Dose Expansion Cohorts, a RP2D will be selected.

3.4 Concomitant Medications, Treatments, and Procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide supportive care except for prohibited medications (see Section 3.4.2). Best supportive care should be provided when necessary for all subjects (including antibiotics, bisphosphonates, receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management including palliative radiotherapy) after consultation with the Sponsor Medical Monitor.

Use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary use of corticosteroids (e.g., prior to computed tomography [CT] to prevent contrast allergies) is acceptable after consultation with the Sponsor Medical Monitor. Use of immunosuppressive medication for the management of SL-279252-related AEs (e.g., prophylaxis in subjects who experience IRRs/CRS, treatment of immune-related toxicities) is permitted.

3.4.1 Tumor Lysis Syndrome Prevention and Treatment Recommendations

Hematologic malignancies are associated with a higher risk of tumor lysis syndrome (TLS). Although TLS has been reported with solid tumors, its occurrence is rare. The incidence of TLS with immune checkpoint inhibitors and costimulatory molecules is not well characterized. TLS was recently reported in a subject with bladder cancer following treatment with atezolizumab [Brunnhoelzl, 2017]. Guidance for identifying subjects at risk and for management of TLS is provided below.

- The risk factors for developing acute TLS after initiation of chemotherapy include uric acid level (>8 mg/deciliter [dL] or 25% increase from baseline), high tumor burden, high lactate dehydrogenase (i.e., LDH ≥2 x ULN), hypercalcemia, elevated creatinine (>1.6 mg/dL), leukocytosis (>50x10^9/liter [L]), and rapidly proliferating drug sensitive neoplasms [Rampello, 2006; Tufan, 2006].

- All subjects with elevated uric acid (>8 mg/dL, or >476 millimole [mmol]/L) should receive prophylaxis with allopurinol or rasburicase, and hydration per standard of care. Blood chemistries should be monitored as indicated. If the constellation of clinical and/or laboratory signs indicate a possibility of developing TLS, subjects should be hospitalized with frequent monitoring of clinical signs and clinical chemistries and treated accordingly. IV hydration should be continued, as needed, in subsequent cycles and subjects should be monitored for fluid overload during this period.

Treatment of TLS should be instituted when appropriate according to institutional guidelines.

3.4.2 Prohibited Medications/Treatments

Subjects must be instructed not to take any medications, including over-the-counter products without first consulting with the investigator. The following medications are prohibited during the study:

- Any investigational anti-cancer therapy not described in this protocol
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy after consultation with the Sponsor Medical Monitor), hormonal therapy for anti-cancer intent, immunotherapy, or biologic therapy for cancer treatment
- Concurrent granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF)
- Immunosuppressive medications for primary prophylaxis against IRRs are not permitted. Subjects who require immunosuppressive medications (e.g., corticosteroids) for management of irAEs or IRRs/CRS should be managed per Toxicity Management Guidelines in Section 3.5.
- Live attenuated vaccines during the study through 30 days after the last dose of SL-279252

3.4.3 Medications to be used with Caution

SL-279252 is a therapeutic protein that may induce the transient release of cytokines including IL-6 which in turn, may inhibit the activity of cytochrome P450 (CYP450) enzymes including CYP3A4 activity [Evers, 2013]. Although not tested clinically, a drug-drug interaction may occur with the coadministration of medications that are CYP450 substrates. Drugs metabolized by CYP450 enzymes may have reduced clearance or an increase in half-life or peak plasma concentration and should be used with caution. There may be an increased risk of side effects for drugs that are CYP450 substrates. Where possible consider substitutions for these medicinal products if therapeutic effects cannot be monitored.

A complete list of drugs that are CYP450 substrates including CYP3A4 substrates is available at: https://drug-interactions.medicine.iu.edu/Main-Table.aspx (Flockhart Table).

3.5 Toxicity Management Guidelines

All AEs should be assessed using NCI-CTCAE v5.0 criteria. **NOTE:** Hereafter in this Section, SL-279252 may be referred to as SL-279252 or as IP. Please see sections 5.5 Physician Availability Required for Administration of SL-279252 and 5.6 Monitoring Dose Administration. **NOTE**: Dose reductions of SL-279252 are not permitted except in the event of rechallenge after Grade 3 CRS as noted in the guideline below.

3.5.1 Management of Infusion-related Reactions

The data from the NHP studies indicate a potential risk for IRRs including CRS in humans dosed with SL-279252. The IRRs that were noted in cynomolgus monkeys were potentially cytokine-mediated as they a) demonstrated dose dependence and b) the severity of clinical symptoms correlated with cytokine level increases in the peripheral blood. It is important to note that the reactions that were noted in monkeys occurred during or immediately after SL-279252 infusion. Given the mechanism of action of SL-279252 (T cells become activated as they recognize tumor antigen), rapid onset of IRRs would be expected but the possibility of delayed reactions cannot be excluded. It is unlikely that SL-279252 infusion reactions are antibody-mediated type I or type 3, allergic HSRs as these reactions would not be expected to demonstrate dose dependence.

Differentiating between IRRs that are due to either the common non-allergic HSRs (e.g., CRS) or the rarer allergic HSRs can be challenging due to overlapping clinical manifestations. There are no specific clinical features (including symptoms and timing of reaction) that can absolutely distinguish between these two entities.

General guidance is provided below for IRRs secondary to both allergic and non-allergic HSRs e.g., CRS. These guidelines are not meant to be prescriptive. Established institutional guidelines should be followed where appropriate.

At the resolution of the event, the entirety of the data including clinical symptoms, response to treatment and laboratory studies should be re-evaluated to determine the final etiology of the event. For purposes of standardized reporting, utilize terms based on best medical judgement of the AE/SAE and the definition found in NCI-CTCAE v5.0 for IRR, allergic reaction, anaphylaxis, and CRS.

Primary prophylaxis against IRRs is not permitted to avoid obscuring a potential safety signal and to enable an assessment of whether pre-medications should be required for all subjects. However, as noted in the guidance below, secondary prophylaxis (i.e., prevention of IRRs following an initial episode) is appropriate and permitted at the discretion of the investigator.

NOTE: In the event of any Grade IRR (including CRS), subjects will be admitted for closer observation until resolution of symptoms.

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Infusion-related Reactions (IRRs) [Rosello, 2017; Porter, 2018]</th></tr>
<tr><td rowspan="5">Infusion or Hypersensitivity Reactions</td><td colspan="2">Acute reactions to the IV administration of biologic agents is not uncommon. Reactions are either allergic reactions to foreign proteins or non-immune reactions. The term HSR is used to describe objectively reproducible signs or symptoms initiated by exposure to a defined stimulus at dose tolerated by a normal person. Allergy is HSR initiated by specific immunological mechanisms. Anaphylaxis is a severe, life threatening HSR. CRS consists of a non-allergic, cytokine mediated HSR. Differentiation between the common non-allergic HRS reactions and the rarer allergic HSR reactions can be challenging due to overlapping clinical manifestations. Fever, chills, rigors, headache, arthralgias, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate and blood pressure are manifestations of common acute infusion reactions. Proinflammatory cytokines such as TNF-α and IL-6 may play a role in these reactions. Symptoms more suggestive of allergic HSR include generalized pruritus, urticaria, wheezing, frequent coughing, and anaphylactic symptoms. Subjects must be monitored for signs and symptoms of IRRs with prompt institution of treatment.</td></tr>
<tr><td>Severity</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Infusion interruption not indicated
• Admit to hospital for close observation until resolution of symptoms.
• Consider pre-medication (antipyretics, histamine (H)1 and H2 anti-histamines) for subsequent infusions per investigator/institutional guidelines</td></tr>
<tr><td>Grade 2</td><td>• Temporarily interrupt IP, or decrease the rate of the infusion by 50%, until resolution of the event.
• Begin IV infusion of normal saline and treat with antipyretics, histamine 1 and 2 (H1 and H2) anti-histamines. Corticosteroids and/or bronchodilator therapy may also be administered as appropriate. Monitor subject until resolution of symptoms.
• If the infusion is interrupted, then restart the infusion at no more than 50% of the rate at which the reaction symptoms occurred
• If no further symptoms are experienced, infusion rate may be escalated at intervals and increments as clinically appropriate
• If symptoms recur, then no further investigational product (IP) will be administered at this visit.
• Admit to hospital for close observation until resolution of symptoms.
• The following prophylactic pre-medications are recommended for future infusions: antipyretics, anti-histamines with/without corticosteroids per institutional guidelines</td></tr>
<tr><td>Grade 3</td><td>• Immediately discontinue infusion.
• Begin IV infusion of normal saline and treat with epinephrine, bronchodilators, diphenhydramine, ranitidine, corticosteroids, oxygen, fluids, vasopressors etc.as indicate and per institutional guidelines. Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed.
• Admit to hospital for close observation until resolution of symptoms.
• Rechallenge should not be attempted in cases of true anaphylaxis. In other cases, once subject has completely recovered, carefully consider if it is safe for the subject to receive IP at the next scheduled dose with pre-medication (e.g., corticosteroids, anti-histamines, antipyretics) and slow infusion (≤ 50% of the rate at which the reaction occurred). If no further symptoms, rate may be escalated at intervals and increments as clinically appropriate. If symptoms recur, permanently discontinue IP</td></tr>
<tr><td>Grade 4</td><td>• Permanently discontinue IP
• Manage severe IRRs per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed
• Admit to hospital for close observation until resolution of symptoms.</td></tr>
</table>

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Cytokine Release Syndrome (CRS) [Rosello, 2017; Porter, 2018]</th></tr>
<tr><td rowspan="4">Cytokine-release</td><td colspan="2">CRS is a non-antigen specific, systemic inflammatory response that occurs as result of high-level immune activation with concomitant elevations of cytokines (e.g., IL-6, IL-10, TNF-α, IL-2, IFNɣ). Clinical features of the syndrome include (but are not confined to) fever, flu-like symptoms, rash, nausea, vomiting, diarrhea, hypotension, tachypnea, transaminitis, hypofibrinogenemia, elevation in D-dimer, hyperbilirubinemia, azotemia, neurologic manifestations. The syndrome can progress to life-threatening capillary leak, hypoxic respiratory failure, vasodilatory shock and end-organ dysfunction. NOTE: CRS may have a similar presentation to a type 1 HSR and may be clinically indistinguishable.</td></tr>
<tr><td>Severity (symptoms)</td><td>Management of CRS</td></tr>
<tr><td>Grade 1</td><td>• Decrease the rate of the infusion by 50%, until resolution of the event
• Maintain IV access. Symptomatic treatment with antipyretics, antiemetics, analgesics, H1/H2 antihistamines as needed; monitor fluid balance; assess for infection. Regularly evaluate for signs of further deterioration
• Admit to hospital for close observation until resolution of symptoms.
• For subsequent infusions, consider pre-medication (e.g., antipyretics, anti-histamines) per institutional guidelines</td></tr>
<tr><td>Grade 2</td><td>• Interrupt IP and do not-restart until symptoms are returned to grade ≤1 for at least 3 days. Once symptoms have resolved, administer dose per next scheduled time point.
• Start IV infusion with normal saline. Administer oxygen if needed. Treat with antipyretics, H1/H2 antagonists (diphenhydramine 50 mg IV plus ranitidine 50 mg IV), and/or methylprednisolone 1-2 mg/kg or equivalent dose of corticosteroid every 6 hours and manage per institutional guidelines. Closely monitor cardiac and other organ functions.
• Admit to hospital for close observation until resolution of symptoms.
• The next two subsequent infusions of SL-279252 (after an event of grade 2 CRS) must be administered in an inpatient setting for prolonged observation (e.g., 24 hours).
• For subsequent infusions, start infusion at 50% rate at which the symptoms occurred and titrate to tolerance. Consider pre-medication with dexamethasone 20 mg, antipyretics, H1/H2 anti-histamines, and manage per institutional guidelines.
• Subjects with extensive comorbidities or those of older age should be treated as for Grade 3. Subjects with worsening symptoms should be treated as for Grade 3</td></tr>
<tr><td>Grade 3</td><td>• Interrupt IP and do not-restart until symptoms are returned to grade ≤1 for at least 3 days. Once symptoms have resolved, administer dose per next scheduled timepoint.
• Admit to hospital for close observation until resolution of symptoms.
• For Grade 3 CRS, may consider rechallenge at the next lower dose level after consultation with medical monitor.
• After a Grade 3 CRS event, subjects must be premedicated with high dose steroids prior to the next infusion of SL-279252.
• If there is no evidence of CRS with the infusion at the reduced dose level, premedication with high dose steroids may be omitted for subsequent infusions.
• The two subsequent infusions of SL-279252 after an event of grade 3 CRS should be administered in an inpatient setting for prolonged observation (e.g., 24 hours).
• Any patient that experiences recurrence of Grade 3 CRS following re-treatment must be permanently discontinued from study treatment.
(Continued on next page)</td></tr>
</table>

	Severity (symptoms)	Management of CRS

Cytokine-release (continued from previous page)	Grade 3 (continued)	• Monitor for organ dysfunction: admit to the intensive care or equivalent for close monitoring and management.
		• Treat hypotension with IV fluid for blood pressure support and/or pressers. Administer oxygen for treatment of hypoxia. Cryoprecipitate or fresh frozen plasma may be required for coagulopathy. Manage per institutional guidelines.
		• Administer tocilizumab at a dose of 8 mg/kg. If clinical improvement does not occur within 24 hours, administer a second dose of tocilizumab.
		• Second-line therapies:
		  • Methylprednisolone 2 mg/kg/day IV tapered over several days. For subjects with severe neurologic symptoms, consider using dexamethasone due to more efficient penetration of the blood-brain barrier.
		  • Anti-TNF-α mAbs (infliximab) or soluble TNF-α receptor (etanercept), or IL-1R-based inhibitors (anakinra).

	Grade 4	• For Grade 4 CRS, permanently discontinue IP
		• Admit to hospital for close observation until resolution of symptoms.
		• Monitor for organ dysfunction: admit to the intensive care or equivalent for close monitoring and management
		• Treat hypotension with IV fluid for blood pressure support and/or pressers. Administer oxygen for treatment of hypoxia. Cryoprecipitate or fresh frozen plasma may be required for coagulopathy. Manage per institutional guidelines.
		• Administer tocilizumab at a dose of 8 mg/kg. If clinical improvement does not occur within 24 hours, administer a second dose of tocilizumab.
		• Second-line therapies:
		  • Methylprednisolone 2 mg/kg/day IV tapered over several days. For subjects with severe neurologic symptoms, consider using dexamethasone due to more efficient penetration of the blood-brain barrier.
		  • Anti-TNF-α mAbs (infliximab) or soluble TNF-α receptor (etanercept), or IL-1R-based inhibitors (anakinra).

3.5.2 Management of irAEs

Adverse Event	General Guidance for Management of Immune-related Adverse Events (irAEs) [Haanen, 2017; Puzanov, 2017; Brahmer, 2018]	
irAEs - General	Guidelines for management of irAEs across body systems are outlined in this section. These guidelines are not meant to be prescriptive. Established institutional guidelines should be followed where appropriate. Severity of irAE are categorized according to NCI CTCAEv5. Limitations of classification and grading by CTCAEv5 for specific irAEs may be encountered. Based on the severity of the irAE, the IP may either be continued, held or permanently discontinued. Management relies heavily on corticosteroids and other immunomodulatory agents. Generally, the decision on IP and institution of immunosuppressive therapy (corticosteroid therapy) can be approached as noted below. However, treatment should be individualized depending on the subject's medical history, the nature and severity of the AE, co-morbidities, and ability to tolerate corticosteroids. When starting corticosteroid therapy, consider initiating proton pump inhibitors for gastrointestinal (GI) toxicity prophylaxis. Once toxicity has improved to ≤ Grade 1 AE, start tapering corticosteroid therapy over a 4 to 6-week period. Add pneumocystis pneumonia prophylaxis (cotrimoxazole or inhaled pentamidine if cotrimoxazole allergy) if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent). Consider calcium & vitamin D supplementation as per local guidelines.	
	Severity	**Management**
	Grade 1	• IP is continued, and treatment with corticosteroids is usually not indicated
	Grade 2	• Depending on the nature of the AE, corticosteroids may be indicated. • Start with oral prednisone 0.5-1 mg/kg/day. IP is generally held during corticosteroid therapy and until irAE has resolved to ≤ Grade 1 and corticosteroids have been tapered to ≤ prednisone 10 mg/day (or equivalent) or discontinued. • If IV therapy is required, use methylprednisolone 0.5 – 1 mg/kg/day. If no improvement in symptoms, the dose may be increased to 2 mg/kg/day.
	Grade 3	• Hold IP. • Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone). • If no improvement, consider adding alternative immune suppressant therapy.
	Grade 4	• Permanently discontinue IP and start IV methylprednisolone 1-2 mg/kg/day. • If no improvement, consider adding alternative immunosuppressant.
Adverse Event	**General Guidance for Skin Toxicity**	
Skin Toxicity	Monitor for signs and symptoms of dermatitis (rash and pruritus). Exclude other causes (e.g., infection, drug, another systemic disease or unrelated primary skin disorder). IP must be discontinued if there is any bullous formation (any grade), or if Severe Cutaneous Adverse Reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms) are present. Severity may be based on affected body surface area (BSA), tolerability, morbidity, and duration.	
	Severity (symptoms)	**Management**
	Grade 1 (Skin rash <10% BSA, with or without symptoms)	• Continue IP. • Topical emollients and/or mild-moderate potency topical corticosteroids +/- oral or topical antihistamines for pruritus. • Counsel subject to avoid skin irritants and sun exposure.

	Severity (symptoms)	Management
Skin Toxicity (continued from previous page)	Grade 2 (Rash covers 10% - 30% of BSA with or without symptoms; limiting instrumental activities of daily living (ADL)	• Continue IP. • Treat with moderate-to-high potency topical corticosteroid twice daily and supportive management as above. • If no resolution, interrupt IP until AE has reverted to Grade 1. • Consider initiating systemic steroid as for Grade 3. • Consider dermatology referral and skin biopsy.
	Grade 3 (Rash covering >30% BSA with or without symptoms; limiting self-care ADL, or Grade 2 with substantial symptoms)	• Hold IP. • Consider hospitalization; consult dermatology; monitor extent of rash; consider punch biopsy and clinical photography. • Rule-out systemic hypersensitivity. Treat with high potency topical corticosteroids, topical emollients, and oral antihistamines. • Initiate oral (or IV) steroids: prednisone 0.5-1 mg/kg/day (or equivalent), tapering over 2-4 weeks. • Consult dermatology to determine appropriateness of resuming IP once the dermatitis has resolved to Grade 1 and the dose of prednisone is ≤ 10 mg/day (or equivalent).
	Severity (symptoms)	**Management**
	Grade 4 (Skin sloughing >30% BSA with symptoms e.g., erythema, purpura, epidermal detachment)	• Permanently discontinue IP. • Seek urgent dermatology consult; admit to hospital; consider punch biopsy and clinical photography. • Treat with methylprednisolone 1 – 2 mg/kg/day (or equivalent) with slow taper when the toxicity resolves. **NOTE:** Grade 4 maculopapular rash/dermatitis is not included in CTCAEv5.

<table>
<tr><th>Adverse Event</th><th colspan="3">General Guidance for Gastrointestinal (GI) Toxicity</th></tr>
<tr><td rowspan="6">Gastrointestinal (GI) Toxicity</td><td colspan="3">• Counsel subjects to inform their physician if they experience symptoms that may be related to diarrhea/enterocolitis (e.g., abdominal pain, cramping, increased frequency of bowel movements over baseline, blood in stool, peritoneal signs, fever, ileus).
• Rule out alternative etiologies (e.g., infection, disease progression). Stool microscopy for leukocytes/ova/parasites, calprotectin, lactoferrin, culture, viral polymerase chain reaction (PCR), Clostridium difficile toxin and cryptospordia.
• Sigmoidoscopy/colonoscopy (+/- biopsy) is recommended in subjects with severe diarrhea (Grade 3 or 4) or persistent Grade 2 diarrhea. Subjects with Grade 1 or 2 diarrhea with dehydration, fever, tachycardia or hematochezia would be managed as per Grade 3 or 4. Steroids should be considered in the absence of clear alternative etiology, even for low grade events, to prevent potential progression to higher grade event.
• Use analgesics carefully; they may mask symptoms of perforation and peritonitis. Use antidiarrheal agents with caution (avoid in patients with obstruction, colonic dilation, fever, abdominal tenderness, infectious colitis, moderate to severe inflammation of the colon).</td></tr>
<tr><td colspan="2">Severity (symptoms)</td><td rowspan="2">Management</td></tr>
<tr><td>Diarrhea</td><td>Enterocolitis</td></tr>
<tr><td>Grade 1
(< 4 liquid stools per day over baseline, mild increase in ostomy output compared to baseline)</td><td>Grade 1
(Asymptomatic; clinical or diagnostic observations only; intervention not indicated)</td><td>• Continue IP.
• Monitor closely for worsening symptoms.
• If symptoms persist, start routine work-up.
• Institute symptomatic management: hydration, electrolyte replacement, dietary changes (bland diet advisable, avoid high fiber/lactose diet) and antidiarrheal medication (exercise caution as above).
• Obtain gastroenterology consult for prolonged Grade 1 cases.</td></tr>
<tr><td>Grade 2
(4-6 stools per day over baseline, moderate increase in ostomy output compared to baseline)</td><td>Grade 2(Abdominal pain; mucus or blood in stool)</td><td>• Hold IP.
• Outpatient management, if appropriate; work-up as above for Grade 1. Symptomatic management. If diarrhea only, observe for 2-3 days, and if no improvement, start prednisone 0.5 – 1 mg/kg/day or equivalent.
• If diarrhea and colitis, start prednisone 1 mg/kg/day (or equivalent dose of methylprednisolone). If no improvement, increase to 2 mg/kg/day.
• If subject improves, taper corticosteroids.
• Consider resuming IP when symptoms improved to ≤Grade 1 and corticosteroid is tapered to ≤10 mg/day prednisone or equivalent.</td></tr>
<tr><td colspan="2">Severity (symptoms)</td><td rowspan="2">Management</td></tr>
<tr><td>Diarrhea</td><td>Diarrhea</td></tr>
<tr><td>Grade 3
(≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL)</td><td>Grade 3
(Severe or persistent abdominal pain; fever, ileus, peritoneal signs; medical intervention indicated)</td><td>• Hold IP
• Consider hospitalization; obtain gastroenterology consult, blood and stool work-up, imaging, endoscopy.
• Start methylprednisolone 1–2 mg/kg/day immediately.
• If refractory or no improvement on IV corticosteroids, consider infliximab 5 mg/kg which can be repeated after 2 weeks if needed.
• Consider resuming IP when corticosteroid is tapered to ≤10 mg/day prednisone or equivalent and subject recovers to ≤Grade 1.</td></tr>
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GI Toxicity (continued from previous page)	**Severity**	**Management**
	Grade 4 (Life threatening consequences; urgent intervention indicated)	• Permanently discontinue IP. • Hospitalize; gastroenterology consult; work-up as above. • Start methylprednisolone 1-2 mg/kg/day or equivalent until symptoms improve to Grade 1, then taper. If refractory to steroids, consider infliximab 5 mg/kg (if no perforation, sepsis, tuberculosis (TB), hepatitis, New York Heart Association [NYHA] III/IV congestive heart failure), can repeat 2 weeks later. Other treatment options include mycophenolate mofetil (MMF) or tacrolimus.

Adverse Event	**General Guidance for Hepatotoxicity**	
Hepatotoxicity	Monitor signs, symptoms and laboratory evidence of liver dysfunction. Evaluate alternative etiologies: review medications for hepatotoxic drugs and alcohol history; perform liver screen: hepatitis A, B, C serology, hepatitis E PCR, antinuclear antibody (ANA)/smooth muscle antibody/liver kidney microsomal antibodies /soluble liver antibody/liver-pancreas antigen/liver cytosol iatrogene antibodies, iron studies; consider imaging for metastases/thrombosis. Guidelines are based on elevations in ALT, AST and bilirubin per CTCAEv5. Discontinue IP for Hy's law as follows: in subjects who enroll with AST/ALT/total bilirubin≤ ULN who experience concomitant AST or ALT > 3 x ULN and total bilirubin > 2 x ULN; or in subjects who enroll with AST/ALT/total bilirubin > ULN who experience concomitant AST or ALT > 3 x baseline and total bilirubin > 2 x baseline.	
	Severity	**Management**
	Grade 1	• Continue IP with close monitoring. • Monitor liver function at least weekly; if liver function is stable, reduce frequency of blood tests.
	Grade 2	• Hold IP. • Assessments as above; monitor liver function ~every 3 days; liver biopsy is optional. • If persistent or rising liver chemistries, or significant clinical symptoms, start oral prednisone 0.5-1 mg/kg/day (or equivalent of methylprednisolone) with 4-week taper. • Resume IP when toxicity ≤ G1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.
	Grade 3 or 4	• Grade 3: hold IP; permanently discontinue IP for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin ≤ ULN: AST or ALT > 8 x ULN **or** total bilirubin > 5 x ULN; permanently discontinue IP for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin > ULN: AST or ALT > 8 x baseline **or** total bilirubin > 5 x baseline. Other Grade 3 laboratory abnormalities: re-challenge may be considered only after consultation with hepatologist. • Grade 4: permanently discontinue. • Consider hospitalization; obtain hepatology consult; assessments as above; monitor liver function daily; consider liver biopsy. • Immediately start methylprednisolone 1-2 mg/kg (start with 2 mg/kg for Grade 4) or equivalent. • If refractory after 3 days, consider MMF. • Avoid the use of infliximab in immune mediated hepatitis.

<table>
<tr><td rowspan="4">Pulmonary Toxicity</td><td colspan="2">General Guidance for Pulmonary Toxicity</td></tr>
<tr><td colspan="2">Monitor subjects for signs and symptoms of pneumonitis or interstitial lung disease (new onset or worsening shortness of breath or cough). Initial work-up may include clinical evaluation, chest X-ray, pulse oximetry (resting and exertion), laboratory work-up, screen for viral, opportunistic or bacterial infections depending on the clinical context. High resolution computed tomography (CT) scan +/- bronchoscopy and bronchoalveolar lavage (BAL).</td></tr>
<tr><td>Severity</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Consider holding IP as clinically appropriate and during diagnostic work-up.
• Monitor every 2 – 3 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up as clinically indicated.
• Consider pulmonary and infectious disease consult.
• May resume IP with radiographic evidence of improvement or resolution. If no improvement, should treat as Grade 2.
• Monitor patients weekly with history, physician examination, pulse oximetry, and chest X-ray if required.</td></tr>
<tr><td>Grade 2</td><td>• Hold IP until resolution to baseline.
• If Grade 2 toxicity improves to baseline, then consider re-challenge if symptoms and imaging abnormalities resolve and corticosteroids ≤10 mg/day prednisone or equivalent.
• Monitor symptoms daily and consider hospitalization.
• Institute work-up – high resolution CT +/- bronchoscopy and BAL pending clinical status, repeat chest X-ray weekly and baseline bloods, pulmonary function tests (PFTs) including transfer factor for carbon monoxide. Obtain pulmonary and infectious disease consult.
• Start antibiotics if suspicion of infection (fever, C reactive protein (CRP), neutrophil counts).
• If no evidence of infection or no improvement with antibiotics after 48 hours, add in oral prednisone 1 mg/kg/day.
• If no improvement after 48 hours of oral prednisone, manage as per Grade 3 or 4.
• Once improved to baseline, wean steroids over at least 6 weeks, titrate to symptoms.</td></tr>
<tr><td>Grade 3 or 4</td><td>• Permanently discontinue IP.
• Promptly initiate methylprednisolone 2 to 4 mg/kg/day or equivalent.
• Hospitalize; provide supportive care (oxygen, etc.); obtain baseline tests as above including high resolution CT and respiratory review +/- bronchoscopy and BAL pending appearances. Obtain pulmonary and infectious disease consult.
• Initiate empiric antibiotics.
• If no improvement or worsening after 48 hours, add infliximab at 5 mg/kg, or MMF (if concurrent hepatotoxicity).
• Continue with IV steroids and wean as clinically indicated.
• Once improved to baseline, wean steroids over at least 8 weeks.</td></tr>
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<tr><th>Adverse Event</th><th colspan="2">General Guidance for Nephrotoxicity</th></tr>
<tr><td rowspan="4">Nephrotoxicity</td><td colspan="2">Monitor serum creatinine and urea prior to every dose. Stop nephrotoxic drugs (including over the counter medications), rule out infection, urinary tract obstruction and correcting hypovolemia. Withhold IP in the event of significant renal dysfunction; consider the use of systemic corticosteroids therapy (0.5–2 mg/kg methylprednisolone or equivalent) – dose and schedule should be individualized and based on grade. Taper corticosteroids when creatinine improves to Grade 1. In the event of severe renal dysfunction, a nephrologist should be consulted. Reflex renal biopsy should be discouraged until steroid treatment has been attempted. Toxicity grading is based on increase in creatinine level as per CTCAEv5.</td></tr>
<tr><td>Severity</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Initiate work-up and monitor closely.
• Alternatively, consider temporarily holding IP, pending consideration of potential alternative etiologies and baseline renal function.</td></tr>
<tr><td>Grade 2</td><td>• Hold IP; consider resuming when creatinine decreased to ≤ Grade 1 and steroids have been tapered.
• Discontinue IP for persistent or recurrent elevation.
• For persistent creatinine elevation with no other identifiable causes, start prednisone 0.5-1 mg/kg/day or equivalent.</td></tr>
<tr><td>Grade 3

Grade 4</td><td>• Hold IP.
• Start prednisone 1-2 mg/kg/day or equivalent.
• Consider resuming treatment if Grade 3 resolves and cause of event is confirmed.
• Discontinue IP permanently for persistent or recurrent elevation of serum creatinine and urea.
• Permanently discontinue IP. Start methylprednisolone 1-2 mg/kg/day or equivalent.</td></tr>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Endocrine Toxicity</th></tr>
<tr><td>Endocrine Toxicity</td><td colspan="2">• Monitor subject for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. Severe mass effect symptoms (severe headache, any visual disturbances) or severe hypoadrenalism (hypotension, severe electrolyte disturbances) are observed with hypophysitis (observed with anti-CTLA4 therapy; very rare with PD-1/L1 inhibitor therapy. Perform magnetic resonance imaging (MRI) to visualize the pituitary gland and rule out any alternative etiology (e.g., disease progression including brain metastases, infection).
• Consult endocrinologist.
Evaluate thyroid function (thyroid stimulating hormone [TSH], free thyroxine [T]3, free T4) and other relevant endocrine labs (e.g., blood glucose, cortisol, sex hormones) depending on suspected endocrinopathy. Falling TSH across 2 measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements (9 am cortisol) should be performed. Iodine from CT scans may impact thyroid function tests (TFTs). If a subject has an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing (e.g., anti-thyroid antibodies for thyroid dysfunction, C-peptide and antibodies against glutamic acid decarboxylase and islet cell antibodies should be measured to distinguish between type 1 and 2 diabetes mellitus [DM]).</td></tr>
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Adverse Event	Endocrine Toxicity		
Hypothyroidism	**Severity**	**Management**	
	Grade 1 or 2	• Continue IP	
	Grade 3 or 4	• Hold IP for ≥ Grade 3 and consider restarting when symptoms under control. • Check anti-TSH receptor antibodies, anti-thyroid peroxidase (TPO) antibody, nuclear medicine thyroid uptake scan. • Propranolol or atenolol for symptoms; consider thionamide (carbimazole, methimazole, propylthiouracil [PTU]) if anti-TSH receptor antibody positive. • Consider hospitalization and initiate prednisone 0.5–2 mg/kg or equivalent, with gradual taper for painful thyroiditis, severe symptoms or thyroid storm. • Introduce thyroid replacement if patient develops hypothyroidism.	
Hyperthyroidism (differential diagnosis includes thyroiditis, Grave's disease)	Grade 1 or 2	• Continue IP	
	Grade 3 or 4	• Hold IP for ≥ Grade 3 and consider restarting when symptoms under control. • Check anti-TSH receptor antibodies, anti-TPO antibody, nuclear medicine thyroid uptake scan. • Propranolol or atenolol for symptoms; consider thionamide (carbimazole, methimazole, PTU) if anti-TSH receptor antibody positive. • Consider hospitalization and initiate prednisone 0.5–2 mg/kg or equivalent, with gradual taper for painful thyroiditis, severe symptoms or thyroid storm. • Introduce thyroid replacement if patient develops hypothyroidism.	
Hypophysitis	Grade 1	• Continue IP.	
	Grade 2 or greater	• Hold IP for any ≥ Grade 2. • Treatment consisting of hormone replacement therapy for adrenal insufficiency, central hypothyroidism, central hypogonadism should be instituted immediately. • For life threatening symptoms (e.g., adrenal crisis, severe headache, visual field defect): hospitalize and treat with prednisone 1 mg/kg/day or equivalent or higher doses of methylprednisolone, followed by gradual taper. Manage adrenal crisis per standard guidelines. Replace thyroid hormone after corticosteroids have been initiated.	
Adrenal Insufficiency	Grade 1	• Continue IP.	
	Grade 2 or greater	• Hold until subject is stabilized on replacement hormone therapy prednisone or hydrocortisone as per standard practice. • May require mineralocorticoid replacement. Titrate as symptoms dictate. • With Grade 2-4, administer stress dose corticosteroids at presentation with gradual taper down to maintenance.	
Diabetes Mellitus **(Type 1 or Type 2)**	**Note**	**Clinical Signs**	**Management**
	Even subjects with Type 2 Diabetes mellitus (DM) may develop ketoacidosis, an infrequent event	DM with diabetic ketoacidosis	• Hold IP; hospitalize and initiate treatment per standard guidelines. • Once the subject has been regulated with insulin substitution, consider restarting IP
		DM without ketoacidosis	• Hold IP for hyperglycemia ≥ Grade 3 • Once the subject has been regulated with insulin substitution, consider restarting IP

<table>
<tr><th>Adverse Event</th><th colspan="3">General Guidance for Ocular Toxicity</th></tr>
<tr><td rowspan="6">Ocular Toxicity</td><td colspan="3">Counsel all subjects to inform their healthcare provider immediately if they experience ocular symptoms. Evaluate under guidance of ophthalmology. Ocular irAEs are many times seen in the context of other organ irAEs. High level of clinical suspicion as symptoms may not always be associated with severity. Treatment depends on severity, with topical corticosteroids in the case of episcleritis and anterior uveitis, and systemic corticosteroids in the case of severe ocular inflammation and orbital inflammation. Intravitreal anti-vascular endothelial growth is indicated for choroidal neovascularization. Unlike anterior uveitis, posterior uveitis can be asymptomatic but nonetheless, proceed to visual loss.</td></tr>
<tr><td colspan="2">Severity (symptoms)</td><td rowspan="2">Management</td></tr>
<tr><td>Uveitis/Iritis</td><td>Episcleritis</td></tr>
<tr><td>Grade 1
(Asymptomatic anterior uveitis with trace cells)</td><td>Grade 1
(No change in vision from baseline)</td><td>• Continue IP
• Ophthalmology referral within 1 week.
• Start lubrication drops (artificial tears).</td></tr>
<tr><td>Grade 2
(Anterior uveitis with 1+ or 2+ cells; medical intervention required)</td><td>Grade 2
(Symptomatic; moderate decrease in visual acuity; limiting instrumental ADL)</td><td>• Hold IP
• Urgent ophthalmology referral; coordinate treatment with ophthalmologist (topical steroids, cycloplegic agents, systemic corticosteroids).
• May resume IP after returned to ≤ Grade 1 and off systemic steroids indicated for ocular side effects, or once corticosteroids for other concurrent irAE are reduced to ≤10mg/day prednisone or equivalent.
Continued topical/ocular steroids are permitted when resuming therapy to manage and minimize local toxicity.</td></tr>
<tr><td>Grade 3
(Anterior uveitis with ≥3+ cells; posterior or pan-uveitis)</td><td>Grade 3
(Symptomatic with marked decrease in visual acuity; limiting self-care ADL)</td><td>• Permanently discontinue IP
• Urgent ophthalmology referral.
• Systemic corticosteroids and intravitreal/periocular corticosteroids/topical steroid treatment as recommended by ophthalmologist with cycloplegic agents.
• Consider infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment.</td></tr>
<tr><td>Grade 4
(Best corrected visual acuity of 20/200 or worse)</td><td>Grade 4
(Best corrected visual acuity of 20/200 or worse)</td><td>• Permanently discontinue IP
• Emergent ophthalmology referral.
• Systemic corticosteroids (prednisone 1-2 mg/kg or equivalent dose of methylprednisolone) and intravitreal/periocular corticosteroids/topical steroid treatment as recommended by ophthalmologist with cycloplegic agents.
• Consider infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment.</td></tr>
<tr><td colspan="2">Blepharitis</td><td>• There is no formal grading system for blepharitis. Treat with warm compresses and lubrication drops.
• Continue therapy unless persistent and serious.</td></tr>
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Adverse Event	General Guidance for Cardiotoxicity	
Cardiotoxicity	Early consultation with a cardiologist is recommended. Obtain baseline electrocardiogram (ECG). All grades warrant work-up: ECG, creatine kinase (CK), creatine kinase – muscle/brain (CK-MB), troponin, brain natriuretic peptide, echocardiogram (ECHO), chest X-ray; additional testing as guided by cardiologist. High dose corticosteroids should be instituted rapidly if immune-mediated cardiotoxicity is suspected. Escalation to other immunosuppressive drugs, such as infliximab, MMF, antithymocyte globulin (ATG) may be necessary if symptoms do not promptly respond to steroids.	
	Severity	**Management**
	Grade 1	• Hold IP • Initiate diagnostic work-up; resume IP if symptoms resolve; permanently discontinue IP if AE worsens or does not improve.
	Grade 2 or greater	• Permanently discontinue IP • Treat with high-dose corticosteroids (1-2 mg/kg prednisone) until improved to ≤ Grade 1 with gradual taper. • Manage cardiac symptoms according to American College of Cardiology /American Heart Association guidelines and with guidance from cardiology. • Immediate transfer to cardiac care unit should be considered for subjects with elevated troponin or conduction abnormalities. • In subjects without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g/day) and the addition of other immunosuppressive agents (MMF, infliximab, ATG).
Adverse Event	**General Guidance for Neurotoxicity**	
Neurotoxicity	Monitor for symptoms of confusion, altered behavior, headaches, seizures, short term memory loss, depressed level of consciousness, focal weakness, speech abnormality etc. Neurology consultation. Work-up to include, brain MRI w/wo contrast, lumbar puncture for cerebrospinal (CSF) analysis, electroencephalogram to evaluate for subclinical seizures, blood tests (complete blood count [CBC], comprehensive metabolic panel, erythrocyte sedimentation rate [ESR], CRP, anti-neutrophil cytoplasmic antibodies [ANCA], TFTs, treponema pallidum immobilization and thyroglobulin).	
	Severity	**Management**
	Grade 1	• Hold IP • Initiate diagnostic work-up; consider permanent discontinuation of IP if AE worsens or does not improve.
	Grade 2	• Hold IP • Start methylprednisolone 0.5-1.0 mg/kg/day (or equivalent) once infection has been excluded. • Consider permanent discontinuation of IP if AE worsens or does not improve.
	Severity	**Management**
	Grade 3	• Permanently discontinue IP • Start methylprednisolone 1-2 mg/kg/day (or equivalent) and prophylactic antibiotics. • Consider plasmapheresis if no improvement or symptoms worsen after 3 days.
	Grade 4	• Permanently discontinue IP • Start methylprednisolone 1-2 mg/kg/day (or equivalent) and prophylactic antibiotics. • Consider plasmapheresis if no improvement or symptoms worsen after 3 days. • Contact intensive care unit

	General Guidance for Myasthenia Gravis	
Myasthenia Gravis	Neurological consultation. All grades warrant work up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise. Check acetylcholine receptor (AchR) and anti-striated muscle antibodies in blood. If AchR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood. Monitor PFTs with negative inspiratory force and vital capacity (NIF/VC). Consider magnetic resonance imaging (MRI) brain to rule out central nervous system (CNS) involvement by malignancy or alternate diagnosis. Check creatine phosphokinase, aldolase, ESR, CRP for possible concurrent myositis. Rule out concomitant myocarditis.	
	Severity	**Management**
	Grade 1	• Continue IP • Consider permanent discontinuation if AE worsens or does not improve.
	Grade 2	• Hold IP; • Discontinue permanently if AE worsens or does not improve; may resume only if symptoms resolve. • Pyridostigmine starting at 30 mg oral 3 times per day (TID) and gradually increase to maximum of 120 mg oral 4 times per day (QID) as tolerated and based on symptoms. • Administer prednisone 1-1.5 mg/kg/day orally and wean based on symptom improvement.
	Grade 3 or 4	• Permanently discontinue IP • Hospitalize, may need intensive care unit (ICU)-level monitoring. • Frequent pulmonary function assessment and daily neuro review. • Treat with methylprednisolone 1-2 mg/kg/day and IV immunoglobulin (IVIG) (0.4 gm/kg/day x 5 days) or plasmapheresis x 5 days.
Guillain-Barre Syndrome	**General Guidance for Guillain-Barre Syndrome (GBS)**	
	Neurological consultation. All grades warrant work up and intervention given potential to lead to respiratory compromise. Obtain MRI spine w/wo contrast to rule out compressive lesion; perform lumbar puncture for CSF analysis; check serum antibody tests for GBS variants (GQ1b for Miller Fisher variant); PFTs (NIF/VC), and electrodiagnostic studies to evaluate polyneuropathy.	
	Severity	**Management**
	Grade 1	• Continue IP; Consider permanent discontinuation of IP if AE worsens or does not improve
	Grade 2 or higher	• Discontinue IP. • Admit to inpatient unit with capability for rapid transfer to ICU-level monitoring. Frequent neuro review and pulmonary function assessment. • Non-opioid management of neuropathic pain. • Start IVIG (0.4 gm/kg/day x 5 days for a total dose of 2 gm/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic GBS, however, in immunotherapy-related forms, a trial is reasonable (methylprednisolone 2 – 4 mg/kg/day followed by slow taper). • Pulse steroid dosing may also be considered along with IVIG or plasmapheresis.

Adverse Event	General Guidance for Hematologic Toxicity	
Autoimmune Hemolytic Anemia	Although rare, hematologic irAEs have been described (case reports of hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, myelodysplasia, and hemophilia A) with intracerebral pathogenicity index. A hematologic irAE needs to be distinguished from transient changes in laboratory values that can occur during initiation of an immune response (e.g., lymphocytosis, eosinophilia, neutrophilia, monocytosis can be observed following treatment). Development of persistent or progressive cytopenias should prompt evaluation of potential causes. In cases where an obvious cause cannot be identified, an autoimmune cause should be considered and investigated accordingly. Since the CTCAE definition of thrombocytopenia describes absolute platelet levels rather than a change in cell number, it is not a reliable tool for evaluating potentially life-threatening cytopenias.	
	Severity	**Management**
	Grade 1	• Continue IP with close clinical follow-up and laboratory evaluation
	Grade 2	• Hold IP; consider permanent discontinuation. • Prednisone 0.5-1 mg/kg/day or equivalent.
	Grade 3	• Permanently discontinue IP. • Prednisone 1-2 mg/kg/day or equivalents (oral or IV depending on symptoms and speed of development). • Hematology consult; consider hospitalization, transfusion per existing guidelines (minimum number of units to relieve symptoms of anemia or to return subject to safe Hgb range), folic acid supplementation.
	Grade 4	• Permanently discontinue IP. • Prednisone 1-2 mg/kg/day; if no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine, infliximab, MMF, ATG. • Hospitalize; hematology consult; transfuse per existing guidelines.
Immune Thrombocytopenia	**Severity**	**Management**
	Grade 1	• Continue IP with close clinical follow-up and laboratory evaluation.
	Grade 2	• Hold IP until AE has reverted to Grade 1. • Administer oral prednisone 1 mg/kg per day (dosage range, 0.5 – 2 mg/kg per day) for 2-4 weeks after which time this medication should be gradually tapered to lowest effective dose. • IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.
	Grade 3 or 4	• Hold IP until AE has reverted to Grade 1. Hematology consult. • Prednisone 1-2 mg/kg/day or equivalent. • IVIG 1 g/kg may be used with corticosteroids when a more rapid increase in platelet count is required. This dosage may be repeated if necessary. • If treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression

Acquired Hemophilia	**Severity**	**Management**
	Grade 1	• Hold IP and discuss resumption only after considering the risk and benefits. • Administer prednisone 0.5 – 1 mg/kg/day. • Transfusion support as required. • Hematology consult.
	Grade 2	• Hold IP and discuss resumption only after considering the risk and benefits. • Hematology consult. • Administer factor replacement (choice based on presence or absence of inhibitor) • Administer prednisone 1 mg/kg/day +/- rituximab (dose 375 mg/square meter [m^2] weekly x 4 weeks) and/or cyclophosphamide 1-2 mg/kg/day. • Transfusion support as required.
	Grade 3 or 4	• Permanently discontinue IP. • Hospitalize; hematology consult; transfusion support as required. • Administer factor replacement (choice based on Bethesda units' level of inhibitor); bypassing agents may be used. • Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms) +/- rituximab (dose 375 mg/m^2 weekly x 4 weeks) and/or cyclophosphamide 1-2 mg/kg/day. If worsening or no improvement add cyclosporine, or immunosuppression/immunoadsorption.
Adverse Event	**General Guidance for Musculoskeletal Toxicity**	
Musculoskeletal Toxicity	Complete rheumatologic history and examination. Obtain CK and CK-MB. Consider autoimmune blood panel including ANA, rheumatoid factor, anti-cyclic citrullinated peptide, ESR and CRP. If symptoms are suggestive of reactive arthritis or affect the spine, consider HLA-B27 testing. Prior to initiation of immunosuppressive medications, consider obtaining muscle biopsy and other relevant tests (e.g., electromyography). Consider ultrasound and/or MRI of affected joints if clinically indicated. Consider early referral to rheumatologist.	
	Severity	**Management**
	Grade 1	• Continue IP • Initiate analgesia with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDS)
	Grade 2	• Hold IP; • Resume when symptoms are controlled and prednisone ≤ 10mg/day • Escalate analgesia and consider higher doses of NSAIDs as needed. Consult rheumatologist. • If inadequate control, initiate prednisone 10-20 mg/day or equivalent, slow taper according to response. If no improvement after initial 4-6 weeks, treat as Grade 3. If unable to lower corticosteroid dose to below 10 mg/d after 3 months, consider disease- modifying antirheumatic drug (DMARD). Consider intra-articular steroid injections for large joints.

	Severity	Management
Musculoskeletal Toxicity (continued from previous page)	Grade 3	• Hold IP temporarily; • May resume in consultation with rheumatology, if recover to ≤G1. • Initiate oral prednisone 0.5-1 mg/kg. If failure to improve after 4 weeks or worsening in meantime, consider synthetic (methotrexate, leflunomide) or biologic (anti-cytokine therapy such as TNF-α or IL6 receptor inhibitors) DMARD. • Test for viral hepatitis B, C and latent/active TB test prior to DMARD treatment
	Grade 4	• Permanently discontinue IP

3.5.3 Management of Non-irAEs

Severity	Dose Modification	Toxicity Management
Any Grade	**Note:** Dose modifications are not required for AEs not deemed to be related to SL-279252 (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	• Treat accordingly, as per institutional standard
Grade 1	No dose modifications	• Treat accordingly, as per institutional standard
Grade 2	Consider holding SL-279252 until resolution to ≤Grade 1 or baseline.	• Treat accordingly, as per institutional standard
Grade 3	Hold SL-279252 until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume SL-279252 administration. Otherwise, discontinue SL-279252. (**Note**: For Grade 3 labs, decision to hold should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor).	• Treat accordingly, as per institutional standard
Grade 4	Discontinue SL-279252 (**Note**: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor).	• Treat accordingly, as per institutional standard

(Reference: American Society of Clinical Oncology Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.)

3.6 Discontinuation of Investigational Product

SL-279252 should be discontinued by the investigator when a participant meets one of the conditions requiring discontinuation outlined in Section 3.5. The investigator may, however, elect to discontinue SL-279252 for an AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents substantial clinical risk to the subject with continued dosing of the IP. If SL-279252 is permanently discontinued for reasons other than progressive disease or withdrawal of consent, the participant will remain in the study to be evaluated for disease progression, and survival. See the SOA in Section 6 for data to be collected at the time of discontinuation of SL-279252.

3.7 Criteria to Resume Treatment

A participant may resume IP per the guidance outlined in Section 3.5. If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

3.8 Participant Discontinuation/Withdrawals from Study

- A participant may withdraw from the study at any time at his/her own request; or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, an early discontinuation visit should be conducted, as shown in the SOA in Section 6. See SOA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the IP and from the study at that time. Every effort must be made to continue follow-up of participants for protocol-specified safety follow-up procedures to capture AEs, SAEs, and unanticipated problems (UPs).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

3.9 Lost to Follow-up

- A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
    - The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter sent to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered as lost to follow up and withdrawn from the study.

3.10 Premature Termination or Suspension of Study

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to investigators, the Food and Drug Administration (FDA), Health Canada, European Medicines Agency and other regulatory authorities. If the study is prematurely terminated or suspended, the investigator will promptly inform the Institutional Review Board/Institutional Ethics Board (IRB/IEC) and will provide the reason(s) for the termination or suspension. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected or destroyed and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further development of the IP
- Determination of unexpected, significant, or unacceptable risk to participants

3.11 Duration of Treatment

In the absence of treatment delays due to AE(s), treatment may continue until one of the following criteria applies:

- Disease progression per iRECIST or RECIL 2017; **NOTE**: See Section 8.3 for criteria allowing for continuing treatment past initial progression.
- 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

All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The investigator should immediately notify PrimeVigilance upon knowledge of pregnancy (Section 7.6).

The investigator may consider discontinuing IP after agreement with the Sponsor if a subject has achieved maximal clinical benefit (a durable CR or PR or SD of >6 months). The subject will be followed until confirmed disease progression as per protocol. Subject may be eligible for treatment past progression if they meet criteria as outlined in Section 8.3.

Impact of ADA on clinical efficacy (non-response or loss of response to the IP) and safety (product specific immunogenicity risk) will be evaluated and reported on an on-going basis once a validated ADA assay becomes available. If a subject develops ADA, the Sponsor and investigator may take into consideration these factors in assessing the duration of the therapy.

3.12 Duration of Follow-Up

Safety follow-up is at least 90 days after the last dose of SL-279252 (Section 6). Subjects who are withdrawn from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE. Participants who permanently discontinue IP for reasons other than progression will continue with disease assessments until progression (per iRECIST or RECIL) or start of another anti-cancer therapy. Participants who discontinue IP for any reason other than withdrawal of consent will be followed for survival.

3.13 End-of Study Definition

The end-of-study is defined as the point of final data capture (the point at which all required data has been collected to answer the research questions in the protocol). At least 3 months of follow up from the last subject enrolled is required.

4. STUDY POPULATION

4.1 Trial Participants

Participants with advanced stage solid tumors or lymphomas of the histologic types described below may be considered for enrollment in the study if they meet all the eligibility criteria stated in Sections 4.2 and 4.3. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.2 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply.

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.

2. Subject has a histologically confirmed diagnosis of one of the following unresectable locally advanced or metastatic malignancies: melanoma, non-small cell lung cancer (squamous, adeno, or adeno-squamous), urothelial cancer, squamous cell carcinoma of the head and neck, squamous cell cervical cancer, gastric or gastro-esophageal junction adenocarcinoma, squamous cell carcinoma of the anal canal, squamous cell carcinoma of the skin, renal cell cancer, Hodgkin's lymphoma, and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding CNS malignancies. MSI and MMRD testing results as per institution is acceptable.

   - Head and neck cancers: Subjects must have primary tumor locations in the oropharynx, oral cavity, hypopharynx, or larynx. Primary tumor sites of nasopharynx, maxillary sinus, paranasal, and unknown primary are excluded.
   - Non-small cell lung cancers: Subjects with a known EGFR sensitizing (activating) mutation or an ALK fusion are excluded.
   - Melanoma: Subjects with a diagnosis of uveal or ocular melanoma are excluded.

3. Eligible subjects must have tumors expressing PD-L1 $\geq$1% by tumor proportion score (TPS) or combined proportion score (CPS) as determined by a local laboratory.

   - This criteria does not apply to subjects with a diagnosis of melanoma, renal cell carcinoma, Hodgkin's lymphoma and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors.

4. Subject must have received, been intolerant to, or is ineligible for standard therapy (per local guidelines and approvals) or have a malignancy for which there is no approved therapy considered standard of care.

5. Age 18 years and older.

6. Has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

7. Has measurable disease by iRECIST (solid tumors) or RECIL 2017 (lymphoma). Refer to Appendix Sections 16.6 and 16.7 for details on criteria of measurable disease.

8. Has life expectancy of greater than 12 weeks.

9. Laboratory values must meet the following criteria.

Laboratory parameter	Threshold value
Absolute lymphocyte count (ALC)	$\geq 0.8 \times 10^9$/liter (L)
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L without growth factor support

Platelet count	≥ 50 x 10^9/L
Hemoglobin (Hgb)	> 9.0 g/dL with no blood transfusions for at least 5 days prior to D1 of IP.
Creatinine clearance (CrCl)	≥ 30 milliliter (mL)/min (using modified Cockcroft-Gault formula; Appendix Section 16.5)
ALT/AST	≤ 3 x ULN
Total bilirubin	≤ 1.5 x ULN; subjects with isolated indirect hyperbilirubinemia are permitted if direct bilirubin ratio is <35% and total bilirubin is ≤ 3.0 x ULN
Left ventricular ejection fraction (LVEF) by ECHO	≥ Lower limit of normal (LLN) per institutional threshold If LLN is not defined for a given institution, then ejection fraction must be ≥50 %

10. Females of child bearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of D1 of IP. **NOTE**: FCBP unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally postmenopausal for at least 12 consecutive months (see Appendix Section 16.2 for additional details). Documentation of postmenopausal status must be provided. FCBP should use an acceptable method of contraception (see Appendix Section 16.2) to avoid pregnancy during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of IP. FCBP must start using acceptable contraception at least 14 days prior to D1 of IP.
11. Male subjects with female partners must have azoospermia from a prior vasectomy or underlying medical condition or agree to use an acceptable method of contraception during treatment and for 30 days (which exceeds 5 half-lives) after last dose of SL-279252 (see Appendix 16.2). Male subjects of reproductive potential must start using acceptable contraception at least 14 days prior to D1 of treatment with SL-279252 as per Appendix Section 16.2.
12. All AEs resulting from prior anti-cancer immunotherapy have resolved (**NOTE**: exceptions include alopecia, vitiligo, and endocrinopathies adequately treated with hormone replacement).
    - Subjects that were discontinued from prior PD-1/L1 therapy due to immune-related adverse events are not eligible
13. Recovery from toxicities from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (**NOTE**: Low-grade toxicities (e.g., alopecia, ≤ Grade 2 lymphopenia, ≤ Grade 2 hypomagnesemia, ≤ Grade 2 neuropathy) may be allowed at the discretion of the investigator if considered clinically insignificant. Please consult the Sponsor Medical Monitor to discuss these cases).

4.3 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has received more than two prior checkpoint inhibitor containing treatment regimens (regimen refers to either monotherapy or combination immunotherapies) or has had prior treatment with an OX40 agonist.
    - Prior PD-1/L1therapy is not required.
2. Refractory to last PD-1/L1 inhibitor-based therapy which is defined as disease progression within 3 months of treatment initiation.
    - Subjects must have had clinical benefit (stable disease or response) to last PD-1/L1 inhibitor-based therapy for at least three months to be eligible.
3. Any anti-cancer therapy within the time intervals noted below prior to first dose (D1) of SL-279252.

Therapy	Washout period
Chemotherapy	3 weeks
Hormonal therapy	3 weeks
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	3 weeks
Tumor vaccine	4 weeks
Cell-based therapy	8 weeks
Other mAbs or biologic therapies	3 weeks
Major surgery	2 weeks
Radiation (except palliative intent which does not require washout)	2 weeks

4. Concurrent chemotherapy, immunotherapy, biologic or hormonal therapy is prohibited. Concurrent use of hormones for non-cancer related conditions is acceptable.
5. Use of corticosteroids or other immunosuppressive medication, current or within 14 days of D1 of SL-279252 treatment with the following exceptions (i.e., the following are allowed with or within 14 days of D1 of IP):
    - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
    - Physiological doses of replacement steroid (e.g., for adrenal insufficiency) not to exceed 10 mg/day of prednisone or equivalent
    - Steroid premedication for HSRs (e.g., reaction to IV contrast)
6. Receipt of live attenuated vaccine within 28 days of D1 of IP.
7. Active or documented history of autoimmune disease (autoimmune disease does not refer to irAEs; for irAEs see inclusion criteria #11). Exceptions include Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.
8. Active pneumonitis (i.e. drug-induced, idiopathic pulmonary fibrosis, radiation-induced, etc.).
9. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of IP).

10. Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious GI disease associated with diarrhea within 6 months of D1 of IP.
11. Clinically significant or uncontrolled cardiac disease including any of the following:
    - Myocarditis
    - Unstable angina within 6 months from D1 of IP
    - Acute myocardial infarction within 6 months from D1 of IP
    - Uncontrolled hypertension
    - NYHA Class II, III or IV congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy)
12. Untreated CNS or leptomeningeal metastases. Subjects with treated CNS metastases must have completed definitive treatment (radiotherapy and/or surgery) > 2 weeks prior to D1 of IP and no longer require steroids.
13. Women who are breast feeding.
14. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or compromised ability to provide written informed consent.
15. Another malignancy that requires active therapy and that in the opinion of the investigator and Sponsor would interfere with monitoring of radiologic assessments of response to IP.
16. Has undergone allogeneic stem cell transplantation or organ transplantation.
17. Known history or positive test for human immunodeficiency virus, or positive test for hepatitis B (positive for hepatitis B surface antigen [HBsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).

- (**NOTE**: *Hepatitis B virus (HBV)*: Subjects who are hepatitis B core antibody [HBcAb] positive, but HBsAg negative are eligible for enrollment. *HCV*: Subjects who are HCV Ab positive, but HCV RNA negative are eligible for enrollment).

4.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs.

4.5 Accrual Goal

The total sample size expected to complete this study is approximately 78-93 subjects (see Section 9.2.1). Approximately 8-10 clinical sites may participate in SL01-DEL-101. Overall, the study may be completed within approximately 32 months (< 3 years).

5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

Investigational Product Name:	**SL-279252**
Formulation description:	Solution containing 20 mg/mL **SL-279252**
Dosage form:	Supplied as frozen liquid. Recommended storage condition is -85 degrees Celsius (°C) to -65°C and store protected from light.
Unit dose strength(s)/Dose Level(s):	20 mg/mL; in a glass vial (Refer to Section 3.2.4 for dose levels). Refer to the Study Pharmacy Manual (SPM) for further description of drug product.
Physical Description:	SL-279252 solution for infusion is a slightly yellow liquid
Route/ Administration/ Duration:	Delivered as IV solution via a syringe or IV infusion pump. See the Study Pharmacy Manual (SPM) for additional details. Duration of infusion depends on the dose. See Table 5: SL-279252 Dose Escalation Plan in Section 3.2.4 of the protocol.
Dosing instructions:	Determine the number of vials needed based on the assigned dose level (in mg/kg) and the subject's weight (in kg). See the SPM for instructions on IP preparation and information on compatible administration materials. Doses of SL-279252 are to be administered as an IV infusion via an infusion or syringe pump that can ensure precision to at least 0.1 mL/min. Delivery of the prescribed dose within +/- 5% is acceptable.
Secondary Packaging/Quantity/Label type	One Vial of SL-279252/Open Label will be supplied in a carton. See SPM for details.
Manufacturer/ Source of Procurement:	Manufactured for Shattuck Labs

SL-279252 will be provided to sites by the Sponsor. The contents of the label will be in accordance with all applicable regulatory requirements.

5.2 Preparation/Handling/Storage of SL-279252 Investigational Product

5.2.1 Preparation

Standard aseptic technique is acceptable. DO NOT USE a filter for drug preparation.

SL-279252 solution for infusion, 20 mg/mL is supplied as a frozen liquid. Before use, thaw each vial of SL-279252 for infusion (20 mg/mL) overnight under refrigerated conditions protected from light or at room temperature until completely thawed to a clear solution. Following thawing, gently swirl the vial to ensure uniformity. SL-279252 should be diluted in sterile normal saline (0.9%).

The dosing solution of SL-279252 can be held up to 24 hours under refrigerated conditions or 4 hours at room temperature (diluted drug product in bag or syringe) from a stability perspective; but should be used as soon as possible as the product does not contain an antimicrobial preservative. See the SPM for details.

5.2.2 Handling

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Safety Data Sheet (describing the occupational hazards and recommended handling precautions) will be provided to site staff if required by local laws or will otherwise be available from the Sponsor upon request.

In the case of unintentional occupational exposure notify the Sponsor and consult the SPM.

Refer to the SPM for detailed procedures for the disposal and/or return of unused IP.

5.2.3 Administration

Doses of SL-279252 are to be administered as an IV infusion via an infusion pump or syringe pump that can ensure precision to at least 0.1 mL/min for the infusion rate at lower doses.

Infusion rate: The duration of infusion stipulated for each dose is outlined in Table 5: SL-279252 Dose Escalation Plan in Section 3.2.4.

***NOTE**: A physician must be present at the site or immediately available to respond to emergencies during all administrations of IP. A fully functional resuscitation facility must be available. IP must not be administered via IV push or bolus but as an IV infusion using an infusion or syringe pump.*

5.2.4 Storage

SL-279252 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of SL-279252 drug product will be limited to the investigator and authorized site staff. SL-279252 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

SL-279252 drug product vials are to be stored frozen at a temperature range of -85°C to -65°C. Maintenance of a temperature log is required. The drug product should be stored protected from light.

The expiry date, where required, is stated on the product label.

5.3 Product Accountability

In accordance with local regulatory requirements, the investigator or designated site staff must document the amount of IP dispensed and/or administered to study subjects, relevant dates, dilution amounts, SL-279252 lot or batch numbers as on the label, and the amount received from the Sponsor, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

5.4 Dosing and Change in Weight

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. The subject should be dosed according to

their C1D1 weight throughout the study (mg/kg) if there is no significant change in their weight from the weight recorded at the C1D1 visit. A change in weight (i.e., increase or decrease) of the subject by 10% OR greater will require re-calculation of dose (mg/kg).

**Subject weight should be rounded to a whole number prior to calculating the dose to be administered (e.g., 72.5 kg should be rounded up to 73 kg, 72.4 kg should be rounded down to 72 kg).

5.5 Physician Availability Required for Administration of SL-279252

SL-279252 has a risk for inducing CRS and IRRs. A physician must be present on site or immediately available to respond to emergencies every time a subject is administered SL-279252. Fully functional resuscitation facilities must be available and close in proximity to the infusion room. Prompt recognition of AEs and immediate medical attention is essential.

5.6 Monitoring Dose Administration

SL-279252 must be administered in an outpatient oncology treatment center or inpatient unit to enable close monitoring of subjects and proactive management of AEs. As SL-279252 contains only human protein sequences, the chance for SL-279252 to be immunogenic and induce allergic HSRs should be low. However, as with any biologic therapy, infusion or allergic HSRs are possible. Based on the pre-clinical toxicology studies, is anticipated that subjects could also be at risk to develop CRS. Therefore, appropriate drugs and medical equipment to treat acute HSRs and monitoring and management of CRS must be immediately available, and study personnel must be trained to recognize and treat these toxicities. Subjects will be monitored prior to, during, and after infusion of SL-279252. Vital signs will be measured as outlined in the Schedule of Assessments (SOA) in Section 6 and as needed. In the event of any Grade IRR (including CRS), subjects will be admitted for closer observation until resolution of symptoms.

5.7 Treatment of Investigational Product Overdose

In the event of an overdose (defined as administration of a dose and/or schedule greater than the dose and/or schedule that had been studied to date) of SL-279252, the investigator should:

- Contact the Sponsor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least 2 weeks following the infusion. The appropriate AE management guideline should be followed (Section 3.5). The pharmacologic effect (e.g., expansion of lymphocytes) could persist even after the IP is no longer detectable in the serum. Subject should have recovered from toxicities that occurred because of the excess dose before the next scheduled dose is administered.
- Obtain a serum sample for PK analysis within 24 hours of the event if requested by the Sponsor (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the electronic case report form (eCRF)

- If a SAE related to overdose of the IP occurs, it should be documented and reported accordingly (Section 7.5)

Decisions regarding dose interruptions for overdose of IP will be made by the investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the subject.

6. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Assessments (SOA). Protocol waivers or exemptions are not allowed.
- Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time-frame defined in the SOA.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue SL-279252.
- Blood volumes for correlative studies of PK, ADA, cytokines, immunophenotyping, receptor occupancy, cfNA and other laboratory tests *are provided in the Study Laboratory Manual (SLM)*

Please consult the SLM for details and blood volumes required. Estimates of blood requirements for the study are provided in Appendix Section 16.8.

6.1 SOA Table: Schedule 1 Dose Escalation of SL-279252

Dosing Schedule 1		**D1, D8, D15 in cycle 1 over 28 days, thereafter every 2 weeks (D1, D15) over 28 days**																**Post Txt[r]**	**Follow up[s]**
Cycle Length = 28 days		**Cycle 1**								**Cycle 2**				**Cycle 3**		**≥ Cycle 4**			
Procedures/Assessments[b]	**Screen[a]**	**D1**				**D8**	**D15**		D22	**D1**	D2	**D15**	D16	**D1**	**D15**	**D1**	**D15**		
Study Days	**Days -21 to -1**	**1**	*2*	*3, 4*	*5*	**8**	**15**	*16*	*22*	**29**	*30*	**43**	44	**57**	**71**	**85 etc.**	**99 etc.**	**w/in 30 d**	
Informed consent	X																		
Inclusion/exclusion criteria[c]	X	X																	
Demographics & medical history	X																		
Cancer treatment history	X																		
Physical examination	X	X				X	X			X				X		X		X	
Pulse oximetry[d]	X	X[d1]	X[d] 2	X[d2]	X[d2]	X[d1]	X[d1]	X[d2]	X	X[d1]	X[d2]	X[d3]		X[d3]	X[d3]	X[d3]	X[d3]	X	
Vital signs[d]	X	X[d1]	X[d] 2	X [d2]	X[d2]	X[d1]	X[d1]	X[d2]	X	X[d1]	X[d2]	X[d3]		X[d3]	X[d3]	X[d3]	X[d3]	X	
Height	X																		
Weight	X	X					X			X		X		X	X	X	X	X	
ECOG performance status	X	X				X	X			X				X		X		X	
Pregnancy test[e]	X	*Every 8 weeks*												X	*Every 8 weeks*			X	
Hematology profile[f]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry profile[f]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Ferritin		X																	
Coagulation profile[g]	X	X	X			X	X	X	X	X	X	X	X						
Thyroid test[h]	X									X				X		X[h]		X	
Antiviral testing (HBV/HCV)[i]	X																		
Cardiac:12-Lead ECG/ECHO[j]	X																		
Tumor imaging[k]	X		*Every 8 weeks through week 24 (see footnote k)*											X	*(see footnote k)*			X	X
PK/immunogenicity/ cytokine sample(s) in dose escalation cohorts[L]		X	X	X	X		X	X		X	X			X		X		X	
Complement[m]		X	X				X	X		X	X								
Immunophenotyping[m]		X	X		X	X	X	X		X	X	X	X						
Receptor Occupancy[m]		X	X				X	X		X	X	X	X						
SL-279252 administration[n]		X				X	X			X		X		X	X	X	X		
Concomitant medications	X	X	*Continuous Monitoring*															X	
AEs/SAEs[o]	X	X	*Continuous Monitoring: Collect Ad hoc sample of clinical safety labs if IRR or CRS event occurs as outlined in Section 6.6.6.1*															X	
Archival tumor tissue[p]	X																		

Dosing Schedule 1		**D1, D8, D15 in cycle 1 over 28 days, thereafter every 2 weeks (D1, D15) over 28 days**																**Post Txt[r]**	**Follow up[s]**
Cycle Length = 28 days		**Cycle 1**								**Cycle 2**				**Cycle 3**		**≥ Cycle 4**			
Procedures/Assessments[b]	**Screen[a]**	**D1**				**D8**	**D15**		D22	**D1**	D2	**D15**	D16	**D1**	**D15**	**D1**	**D15**		
Study Days	**Days -21 to -1**	**1**	*2*	*3, 4*	*5*	**8**	**15**	*16*	*22*	**29**	*30*	**43**	44	**57**	**71**	**85 etc.**	**99 etc.**	**w/in 30 d**	
Tumor Biopsy[q]	X							X											
Survival																			X

Abbreviations: Txt = Treatment; w/in = within; C = Cycle; D = Day

a. **Screening:** Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-279252: hematology profile, chemistry profile, coagulation profile, pregnancy test. Baseline CT or positron emission tomography (PET)/CT or MRI tumor assessments are required for all subjects within 28 days prior to enrollment. Subjects will be enrolled based on local PD-L1 tumor testing results. Any PD-L1 tumor testing results prior to enrollment are acceptable.

b. **Assessment Window:** A physical exam, weight and ECOG performance status obtained for a subject within 24 hours prior to dosing on Cycle 1, Day 1 is acceptable.With the exception of Screening asessments and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window. Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

c. **Inclusion/Exclusion criteria:** Subjects must meet eligibility criteria prior to first dose of SL-279252 on C1D1.

d. **Vital Signs:** Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been sitting for at least five minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.

   1) **Collect vital signs/pulse oximetry during Cycle 1 on D1, D8, D15 and C2D1**: Predose (within 30 min of starting the infusion) and 15 min (± 5 min), 0.5 hour [hr] (± 5 min), 1 hr (±10 min), 1.5 hr (± 10 min) 2 hr (± 10 min), 4 hr (± 10 min) , and 6 hr (± 10 min) **after SOI.**

   2) **Vital signs/pulse oximetry should be taken once prior to scheduled PK samples on C1D2, C1D3, C1D4, C1D5, C1D16 and C2D2**

   3) **Collect vital signs/pulse oximetry on dosing days ≥ C2D15:** Predose (within 30 min of starting the infusion) and at the end of infusion [EOI] (± 2 min)

e. **Pregnancy Test:** A serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of starting SL-279252. Repeat this test every 8 weeks during SL-279252. *Contraception should be continued for at least 30 days after the last dose of SL-279252.*

f. **Clinical Laboratory Tests (Hematology/Clinical Chemistry):** Clinical laboratory tests will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.6 for list of laboratory test required.

g. **Coagulation Tests:** prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, d-dimer (Cycles 1 and 2 only)

h. **Thyroid Function Test**: TSH, and free T4 tests will be performed at screening, C2D1, C3D1, C4D1 and then every 8 weeks.

i. **Antiviral Testing:** Please see exclusion criterion 17 in Section 4.3.

j. **Cardiac Assessments (obtain within 28 days of first dose): 1) Electrocardiagram (ECG):** 12-lead ECG reading must be performed at screening to serve as baseline for comparison with ECG obtained for safety reason. **2) ECHO:** An ECHO must be performed at screening for comparison with ECHO obtained for safety reason.

k. **Tumor Assessment:** Tumor assessments are required for all subjects within 28 days prior to enrollment. Baseline and on-treatment tumor assessments for solid tumors by iRECIST should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan and positron emission tomography (PET)/CT should be performed only if clinically indicated. Baseline and on-treatment tumor assessment for lymphoma by RECIL 2017 should be done using CT scan with contrast and PET/CT of neck, chest, abdomen, and pelvis and other known sites of disease at each time point. Please refer to Section 8 for requirements regarding disease assessment. Tumor assessments must be performed at screening and at the following intervals until disease progression is confirmed: approximately every 8 weeks through week 24 (e.g., C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 10, 13, 16, 19, 22, 25, 28 and 31), and then every 6 months (prior to cycles 37, cycle 43, etc.) up to conclusion of the study. Confirmatory scans should be performed at least 4 weeks (>28 days), but no longer than 8 weeks after initial documentation of an objective response. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, or disease progression, withdrawal of consent or death.

l. **PK/immunogenicity (i.e., ADA) and cytokine sampling (Dose Escalation Cohorts):** PK, ADA, and cytokine time points for collection of samples are outlined in supplementary tables in Section **6.1.1**. **(Table 6, Table 7 and Table 8).** Blood volumes required are provided in the SLM. PK, ADA, cytokine samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection. If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline. If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

m. **Correlative laboratory studies**: Refer to supplementary **Table 9 for details in Section 6.1.2 plus see the SLM for amount of blood needed.**
- *Complement*
- *Immunophenotyping and Receptor Occupancy*

n. **SL-279252 Administration**: SL-279252 should be administered on D1, D8, and D15 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

o. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. In the event of a continuing SAE or a non-serious AE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

- Ad hoc blood samples for clinical safety labs should be collected for AE related to IRR and/or CRS events as noted in Section 6.6.6.1 and the SLM.

p. **Archival tumor tissue (from most recent biopsy):** Provide formalin-fixed-paraffin-embedded (FFPE) tissue on slides (recommended minimum of 10 slides) or a block of formalin-fixed paraffin embedded (FFPE) tissue (the latter is preferred). Refer to Section 6.9.2.2 and the SLM for details.

q. **Tumor Biopsy**: Paired biopsies (pre- and on-treatment) obtained in subjects who have tumor accessible to core-needle biopsy. The on-treatment biopsy should be obtained during the first cycle on or between D16-D23. On-treatment biopsies of responding or progressing lesions may be obtained for further characterization of the changes in the TME. **Please refer to Section 6.9.2.1 and SLM for details regarding biopsy**.

r. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-279252, or prior to the start of a new therapy, or at the end of study, or if the subject's participation is terminated early. See AE monitoring footnote above.

s. **Follow-Up**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (+/- 14 days) until death, withdrawal of consent or subject is lost to follow-up. Contact may include clinic visit, telephone contact, email or mail to document survival status.

6.1.1 Supplementary Tables for Schedule 1: PK, ADA, Cytokines / Dose Escalation

Table 6: Schedule 1 Dose Escalation Serial PK, ADA, Cytokines (C1/D1 - 96 hrs post dose)

Samples	Predose -30 min (± 5 min)	EOI (+5 min)	SL-279252 PK Intensive Serial Sampling (Dose Escalation Cohorts) / Dosing Schedule 1											
			Time points relate to post EOI / Collect blood for PK at each time point unless otherwise specified[3]											
			0.5 hr (±5 min)	1 hr (±5 min)	1.5 hr (±5 min)	2 hr (±10 min)	3 hr (±10 min)	4 hr (±15 min)	6 hr (±30 min)	8 hr (±30 min)	24 hr (±2 hr)	48 hr (±2 hr)	72 hr (±2 hr)	96 hr (±2 hr)
PK	X[1]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X
Cytokines	X[1]					X			X		X			X
ADA	X[1]													

1. Collect predose samples for ADA, PK and cytokines.
2. EOI sample should be collected within 5 minutes after stopping the infusion. Duration of infusion is subject to change based on emerging data. Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded.
3. Sample collection out to 96 hrs post EOI but emerging data during dose finding may dictate changes in this schedule. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**.

NOTE: The PK, ADA, cytokine samples **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA and cytokine sample collection.

Table 7: Schedule 1 Dose Escalation Serial PK, ADA, Cytokines (C1D15/D16 & C2D1/D2)

Sample	SL-279252 PK Sampling (Dose Escalation Cohorts) / Dosing Schedule 1 / Collect blood for PK time at each time point unless otherwise specified[3]				
	C1/D15 and C2/D1		C1/D15 and C2/D1		C1/D16 and C2/D2
	Predose -30 min (± 5 min)	EOI (+ 5 min)	Time points relate to post EOI[4]		
			2 hr (±10 min)	6 hr (±30 min)	24 hr (± 2 hr)
PK	X[1]	X[2]	X	X	X
Cytokines	X[1]		X	X	X
ADA	X[1]				

1. Collect predose samples for ADA, PK and cytokines.
2. EOI sample should be collected within 5 minutes after stopping the infusion. Duration of infusion may change based on emerging data. Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded.
3. If time points for PK/ADA/cytokines overlap, **see SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**. The PK, ADA, cytokine sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA and cytokine sample collection.
4. Sample collection out to 24 hrs post EOI but emerging data during dose finding may dictate changes in this schedule.

Table 8: Schedule 1 Dose Escalation Serial PK, ADA (C3/D1 and Beyond)

Sample	SL-279252 PK Sampling (Dose Escalation Cohorts) / Dosing Schedule 1 / Collect blood for PK or PK/ADA at each time point as specified				
	C3/D1 and C4/D1	C3/D1 and C4/D1	C3/D1 and C4/D1	D1 of C7, C10, C13[4], and C25	Collect sample for PK/ADA within 7 - 30 days post last dose of SL-279252. If this sample is positive for ADA, then monthly testing for PK/ADA required until resolution of ADA to baseline.
	Predose	EOI	Post EOI	Predose	
	-30 min (± 5min)	(+ 5 min)	6 hr (±30 min)	- 30 min (± 5 min)	
PK	X[1]	X[2]	X	X[1]	
ADA	X[1]			X[1]	

1. Predose sample collected will include analysis of ADA and PK.
2. Collect EOI sample within 5 min after stopping the infusion. Duration of infusion may change based on emerging data. Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded.
3. The PK/ADA sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK sample collection. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions.**
4. If subject has positive ADA test on D1 of cycle 13, then follow up predose PK/ADA samples should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline.

6.1.2 Correlative Sample Time points / Schedule 1 / Dose Escalation

Table 9: Complement, Immunophenotyping, Receptor Occupancy Time Points

Dose Escalation	**C1/D1 & C2/D1**			**C1/D2 & C2/D2**	**C1/D5**	**C1/D8**	**C1/D15 & C2/D15**			**C1/D16 & C2/D16**
Schedule 1	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)	**96 h post EOI** (±2 hr)	**Predose** (-90 to -30 min)	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)
Complement (SC5b-9)[1]	X	X		X			X (C1D15 only)	X (C1D15 only)		X (C1D16 only)
Immunophenotyping[1]	X			X	X	X	X			X
Receptor Occupancy[1]			X						X	

1. Refer to SLM for details. Complement is NOT collected on C2D15 or C2D16.

6.2 SOA Table: Schedule 2 Dose Escalation of SL-279252

Dosing Schedule 2		**Once weekly (D1, D8, D15, D22) X 4 every 28 days**																		**Post Txt[r]**	**Follow Up[s]**
Cycle Length = 28 days		**Cycle 1**								**Cycle 2**						**≥ Cycle 3**					
Procedures/ Assessments[b]	**Screen[a]**	**D1**				**D8**	**D15**		**D22**	**D1**	D2	**D8**	**D 15**	D 16	**D22**	**D1**	**D8**	**D 15**	**D22**		
Study Days	**Days -21 to -1**	**1**	*2*	*3, 4*	*5*	**8**	**15**	*16*	**22**	**29**	*30*	**36**	**43**	*44*	**50**	**57 etc.**	**64 etc.**	**71 etc.**	**78 etc.**	**w/in 30 d**	
Informed consent	X																				
Inclusion/exclusion criteria[c]	X	X																			
Demographics & medical history	X																				
Cancer treatment history	X																				
Physical examination	X	X				X	X		X	X						X				X	
Pulse oximetry[d]	X	X[d1]	X[d2]	X[d2]	X[d2]	X[d1]	X[d1]	X[d2]	X[d1]	X[d1]	X[d2]	X[d1]	X[d3]		X[d3]	X[d3]	X[d3]	X[d3]	X[d3]	X	
Vital signs[d]	X	X[d1]	X[d2]	X [d2]	X[d2]	X[d1]	X[d1]	X[d2]	X[d1]	X[d1]	X[d2]	X[d1]	X[d3]		X[d3]	X[d3]	X[d3]	X[d3]	X[d3]	X	
Height	X																				
Weight	X	X					X			X			X			X		X		X	
ECOG performance status	X	X				X	X		X	X						X				X	
Pregnancy test[e]	X	*Every 8 weeks*														X	*Every 8 weeks*			X	
Hematology profile[f]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry profile[f]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ferritin		X																			
Coagulation profile[g]	X	X	X			X	X	X	X	X	X	X	X	X							
Thyroid test[h]	X									X						X[h]				X	
Antiviral testing (HBV/HCV)[i]	X																				
Cardiac:12-Lead ECG/ECHO[j]	X																				
Tumor imaging[k]	X	*Every 8 weeks through week 24 (see footnote k)*														X	*(see footnote k)*			X	X
PK/immunogenicity/ cytokine sample(s) in dose escalation cohorts[L]		X	X	X	X		X	X		X	X					X				X	
Complement[m]		X	X				X	X		X	X										
Immunophenotyping[m]		X	X		X	X	X	X		X	X		X	X							
Receptor Occupancy[m]		X	X				X	X		X	X		X	X							
SL-279252 administration[n]		X				X	X		X	X		X	X		X	X	X	X	X		
Concomitant meds	X	X	*Continuous monitoring*																	X	
AEs/SAEs[o]	X	X	*Continuous monitoring: Collect Ad hoc sample if IRR or CRS event occurs as outlined in Section 6.6.6.1 and SLM*																	X	

Dosing Schedule 2		**Once weekly (D1, D8, D15, D22) X 4 every 28 days**																		**Post Txt[r]**	**Follow Up[s]**
Cycle Length = 28 days		**Cycle 1**								**Cycle 2**						**≥ Cycle 3**					
Procedures/ Assessments[b]	**Screen[a]**	**D1**				**D8**	**D15**		**D22**	**D1**	D2	**D8**	**D 15**	D 16	**D22**	**D1**	**D8**	**D 15**	**D22**		
Study Days	**Days -21 to -1**	**1**	*2*	*3, 4*	*5*	**8**	**15**	*16*	**22**	**29**	*30*	**36**	**43**	*44*	**50**	**57 etc .**	**64 etc.**	**71 etc.**	**78 etc.**	**w/in 30 d**	
Archival tumor tissue[p]	X																				
Tumor biopsy[q]	X							X													
Survival																					X

Abbreviations: Txt = Treatment; w/in = within; C = Cycle; D = Day

a. **Screening:** Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-279252: hematology profile, chemistry profile, coagulation profile, pregnancy test. Baseline CT or PET/CT or MRI tumor assessments are required for all subjects within 28 days prior to enrollment. Subjects will be enrolled based on local PD-L1 tumor testing results. Any PD-L1 tumor testing results prior to enrollment are acceptable.

b. **Assessment Window:** A physical exam, weight and ECOG performance status obtained for a subject within 24 hours prior to dosing on Cycle 1, Day 1 is acceptable. With the exception of Screening assessments and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window. Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

c. **Inclusion/Exclusion criteria:** Subjects must meet eligibility criteria prior to first dose of SL-279252 on C1/D1.

d. **Vital Signs:** Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been sitting for at least five minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.

   1) **Collect vital signs/pulse oximetry during Cycle 1 on D1, D8, D15, D22 and Cycle 2 D1 and D8**: Predose (within 30 min of starting the infusion) and 15 min (± 5 min), 0.5 hour [hr] (± 5 min), 1 hr (±10 min), 1.5 hr (± 10 min) 2 hr (± 10 min), 4 hr (± 10 min) , and 6 hr (± 10 min) **after SOI.**

   2) **Vital signs/pulse oximetry should be taken once prior to scheduled PK samples on C1D2, C1D3, C1D4, C1D5, C1D16 and C2D2**

   3) **Collect vital signs/pulse oximetry on dosing days ≥ C2D15:** Predose (within 30 min of starting the infusion) and at the end of infusion [EOI] (± 2 min)

e. **Pregnancy Test:** A serum pregnancy test (β-hCG) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of starting SL-279252. Repeat this test every 8 weeks during SL-279252. *Contraception should be continued for at least 30 days after the last dose of SL-279252.*

f. **Clinical Laboratory Tests (Hematology/Clinical Chemistry):** Clinical laboratory tests will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.6 for list of laboratory tests required.

g. **Coagulation Tests:** PT, INR, APTT, fibrinogen, d-dimer (the latter test Cycles 1 and 2 only)

h. **Thyroid Function Test**: TSH, and free T4 tests will be performed at screening, C2D1, C3D1, C4D1 and then every 8 weeks.

i. **Antiviral Testing:** Please see exclusion criterion 17 in Section 4.3.

j. **Cardiac Assessments (obtain within 28 days of first dose): 1) ECG:** 12-lead ECG reading must be performed at screening to serve as baseline for comparison with ECG obtained for safety reason. **2) ECHO**: An ECHO must be obtained at screening to serve as baseline for comparison with ECHO

k. **Tumor Assessment:** Tumor assessments are required for all subjects within 28 days prior to enrollment. Baseline and on-treatment tumor assessments for solid tumors by iRECIST should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan and positron emission tomography (PET)/CT should be performed only if clinically indicated. Baseline and on-treatment tumor assessment for lymphoma by RECIL 2017 should be done using CT scan with contrast and PET/CT of neck, chest, abdomen, and pelvis and other known sites of disease at each time point. Please refer to Section 8 for requirements regarding disease assessment. Tumor assessments must be performed at screening and at the following intervals until disease progression is confirmed: approximately every 8 weeks through week 24 (e.g.,C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 10, 13, 16, 19, 22, 25, 28 and 31), and then every 6 months (prior to cycles 37, cycle 43, etc.) up to conclusion of the study. Confirmatory scans should be performed at least 4 weeks (>28 days), but no longer than 8 weeks after initial documentation of an objective response. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, or disease progression, withdrawal of consent or death.

l. **PK/immunogenicity (i.e., ADA) and cytokine sampling (Dose Escalation Cohorts):** PK, ADA, and cytokine time points for collection are outlined in supplementary tables for PK in Section **6.2.1 (Table 10, Table 11 and Table 12)** plus the SLM. PK, ADA, cytokine samples should not be collected from infusion port for drug delivery. Recommendation is to use a separate line in the opposite arm for sample collection. If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline. If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

m. **Correlative laboratory studies**: Refer to supplementary **Table 13** for details in Section 6.2.2 plus SLM
- *Complement*
- *Immunophenotyping and receptor occupancy*

n. **SL-279252 Administration**: SL-279252 should be administered on D1, D8, D15, and D22 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

o. **Adverse Event (AE) Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. In the event of a continuing SAE or a non-serious AE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

- Ad hoc blood samples for clinical safety labs should be collected for AE related to IRR and/or CRS events as noted in Section 6.6.6.1 and the SLM.

p. **Archival tumor tissue (from most recent biopsy**): Provide formalin-fixed-paraffin-embedded (FFPE) tissue on slides (recommended minimum of 10 slides) or a block of FFPE tissue (the latter is preferred). Refer to Section 6.9.2.2 and the SLM for details.

q. **Tumor Biopsy**: Paired biopsies (pre- and on-treatment) obtained in subjects who have tumor accessible to core-needle biopsy. The on-treatment biopsy should be obtained during the first cycle on or between D16-D23. On-treatment biopsies of responding or progressing lesions may be obtained for further characterization of the changes in the TME. **Please refer to Section 6.9.2.1 and SLM for details regarding biopsy**.

r. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-279252, or prior to the start of a new therapy, or at the end of study, or if the subject's participation is terminated early. See AE monitoring footnote above.

s. **Follow-Up**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (+/- 14 days) until death, withdrawal of consent or subject is lost to follow-up. Contact may include clinic visit, telephone contact, email or mail to document survival status.

6.2.1 Supplementary Tables for Schedule 2: PK, ADA, Cytokines / Dose Escalation

Table 10: Schedule 2 Dose Escalation Serial PK, ADA, Cytokines (C1/D1 - 96 hrs post dose)

Samples	Predose -30 min (± 5 min)	EOI (+5 min)	SL-279252 PK Intensive Serial Sampling (Dose Escalation Cohorts) / Dosing Schedule 2											
			Time points relate to post EOI / Collect blood for PK at each time point unless otherwise specified[3]											
			0.5 hr (±5 min)	1 hr (±5 min)	1.5 hr (±5 min)	2 hr (±10 min)	3 hr (±10 min)	4 hr (±15 min)	6 hr (±30 min)	8 hr (±30 min)	24 hr (±2 hr)	48 hr (±2 hr)	72 hr (±2 hr)	96 hr (±2 hr)
PK	X[1]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X
Cytokines	X[1]					X			X		X			X
ADA	X[1]													

1. Collect predose samples for ADA, PK and cytokines.
2. EOI sample should be collected within 5 minutes after stopping the infusion. Duration of infusion is subject to change based on emerging data. Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded.
3. Sample collection out to 96 hrs post EOI but emerging data during dose finding may dictate changes in this schedule. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**.

NOTE: The PK, ADA, cytokine samples **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA and cytokine sample collection.

Table 11: Schedule 2 Dose Escalation Serial PK, ADA, Cytokines (C1D15/D16 & C2D1/D2)

Sample	SL-279252 PK Sampling (Dose Escalation Cohorts) / Dosing Schedule 2 / Collect blood for PK time at each time point unless otherwise specified[3]				
	C1/D15 and C2/D1		C1/D15 and C2/D1		C1/D16 and C2/D2
	Predose -30 min (± 5 min)	EOI (+ 5 min)	Time points relate to post EOI[4]		
			2 hr (±10 min)	6 hr (±30 min)	24 hr (± 2 hr)
PK	X[1]	X[2]	X	X	X
Cytokines	X[1]		X	X	X
ADA	X[1]				

1. Collect predose samples for ADA, PK and cytokines.
2. EOI sample should be collected within 5 minutes after stopping the infusion. Duration of infusion may change based on emerging data. Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded.
3. If time points for PK/ADA/cytokines overlap, **see SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**. The PK, ADA, cytokine sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA and cytokine sample collection.
4. Sample collection out to 24 hrs post EOI but emerging data during dose finding may dictate changes in this schedule.

Table 12: Schedule 2 Dose Escalation Serial PK, ADA (C3D1 and Beyond)

Sample	SL-279252 PK Sampling (Dose Escalation Cohorts) / Dosing Schedule 2 / Collect blood for PK or PK/ADA at each time point as specified				
	C3/D1 and C4/D1	C3/D1 and C4/D1	C3/D1 and C4/D1	D1 of C7, C10, C13[4], and C25	Collect sample for PK/ADA within 7 - 30 days post last dose of SL-279252. If this sample is positive for ADA, then monthly testing for PK/ADA required until resolution of ADA to baseline.
	Predose	EOI	Post EOI	Predose	
	-30 min (± 5min)	(+ 5 min)	6 hr (±30 min)	- 30 min (± 5 min)	
PK	X[1]	X[2]	X	X[1]	
ADA	X[1]			X[1]	

1. Predose sample collected will include analysis of ADA and PK.
2. Collect EOI sample within 5 min after stopping the infusion. Duration of infusion may change based on emerging data. Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded.
3. The PK/ADA sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK sample collection. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions.**
4. If subject has positive ADA test on D1 of cycle 13, then follow up predose PK/ ADA samples should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline.

6.2.2 Correlative Sample Time points / Schedule 2 / Dose Escalation

Table 13: Complement, Immunophenotyping, Receptor Occupancy Time Points

Dose Escalation	**C1/D1 & C2/D1**			**C1/D2 & C2/D2**	**C1/D5**	**C1/D8**	**C1/D15 & C2/D15**			**C1/D16 & C2/D16**
Schedule 2	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)	**96 h post EOI** (±2 hr)	**Predose** (-90 to -30 min)	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)
Complement (SC5b-9)[1]	X	X		X			X (C1D15 only)	X (C1D15 only)		X (C1D16 only)
Immunophenotyping[1]	X			X	X	X	X			X
Receptor Occupancy[1]			X						X	

1. Refer to SLM for details. Complement is NOT collected on C2D15 or C2D16.

6.3 SOA Table: Schedule 1 Dose Expansion Cohorts

Dosing Schedule 1		**D1, D8, D15 in cycle 1 over 28 days, thereafter every 2 weeks (D1, D15) over 28 days**															**Post Txt[t]**	**Follow Up[u]**
Cycle Length = 28 days		**Cycle 1**						**Cycle 2**			**Cycle 3**		**Cycle 4**		**≥ Cycle 5**			
Procedures/Assessments[b]	**Screen[a]**	**D1**	D2	**D8**	**D15**	D16	D22	**D1**	D2	**D15 D16[s]**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**		
Study Days	**Days -21 to -1**	**1**	*2*	**8**	**15**	*16*	*22*	**29**	*30*	**43**	**57**	**71**	**85 etc.**	**99 etc.**	**113 etc.**	**127 etc.**	**w/in 30 d**	
Informed consent	X																	
Inclusion/exclusion criteria[c]	X	X																
Demographics & medical history	X																	
Cancer treatment history	X																	
Physical examination	X	X		X	X			X			X		X		X		X	
Pulse oximetry[d]	X	X[d1]		X[d1]	X[d1]			X[d2]		X[d2]	X[d2]	X[d2]	X[d2]	X[d2]	X[d2]	X[d2]	X	
Vital signs[d]	X	X[d1]		X[d1]	X[d1]			X[d2]		X[d2]	X[d2]	X[d2]	X[d2]	X[d2]	X[d2]	X[d2]	X	
Height	X																	
Weight	X	X			X			X		X	X	X	X	X	X	X	X	
ECOG performance status	X	X		X	X			X			X		X		X		X	
Pregnancy test[e]	X	*Every 8 weeks*									X	*Every 8 weeks*					X	
Hematology profile[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry profile[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ferritin		X																
Coagulation profile[g]	X	X	X		X	X		X	X									
Thyroid test[h]	X							X			X		X		X[h]		X	
Antiviral testing (HBV/HCV)[i]	X																	
Cardiac:12-Lead ECG/ECHO[j]	X																	
Tumor imaging[k]	X	*Every 8 weeks through week 24 (see footnote k)*									X	*(see footnote k)*			X		X	X
PK/immunogenicity/ cytokine sample(s) in Expansion cohorts[L]		X	X		X	X		X	X		X		X				X	
Complement[m]		X	X		X	X		X	X									
Immunophenotyping[m]		X	X	X	X	X		X	X	X								
Receptor Occupancy[m]		X	X		X	X		X	X	X								
Cell-free nucleic acid (cfNA)[n]		X																
SL-279252 administration[o]		X		X	X			X		X	X	X	X	X	X	X		
Concomitant medications	X	X	*Continuous monitoring*														X	
AEs/SAEs[p]	X	X	*Continuous monitoring: Collect Ad hoc sample if IRR or CRS event occurs as outlined in Section 6.6.6.1 and SLM*														X	
Archival tumor tissue[q]	X																	
Tumor biopsy[r]	X					X												
Survival																		X

Abbreviations: Txt = Treatment; w/in=within; C = Cycle; D = Day

a. **Screening:** Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-279252: hematology profile, chemistry profile, coagulation profile, pregnancy test. Baseline CT or PET/CT or MRI tumor assessments are required for all subjects within 28 days prior to enrollment. Subjects will be enrolled based on local PD-L1 tumor testing results. Any PD-L1 tumor testing results prior to enrollment are acceptable.

b. **Assessment Window:** A physical exam, weight and ECOG performance status obtained for a subject within 24 hours prior to dosing on Cycle 1, Day 1 is acceptable. With the exception of Screening assessements and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window. Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

c. **Inclusion/Exclusion criteria:** Subjects must meet eligibility criteria prior to first dose of SL-279252 on C1/D1.

d. **Vital Signs:** BP, HR, T and respiratory rate (RR) must be measured after the subject has been sitting for at least five min. Pulse oximetry will be collected to coincide with vital sign time points noted below.

   1) **Collect vital signs during Cycle 1 on Day 1, D8, D15**: Predose (within 30 min of starting the infusion) and 15 min (± 5 min), 0.5 hr (± 5 min), 1 hr (±10 min), 1.5 hr (± 10 min) and 2 hr (± 10 min) **after SOI.**

   2) **Collect vital signs on dosing days (Cycles ≥ 2, Days 1 and 15):** Predose (within 30 minutes of starting the infusion) and at the EOI (± 2 min)

e. **Pregnancy Test:** A serum pregnancy test (β-hCG) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of starting SL-279252. Repeat this test every 8 weeks during SL-279252. *Contraception should be continued for at least 30 days after the last dose of SL-279252.*

f. **Clinical Laboratory Tests (Hematology/Clinical Chemistry):** Clinical laboratory tests will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.6 for list of laboratory tests required.

g. **Coagulation Tests:** PT, INR, APTT, fibrinogen, d-dimer (the latter test at screening and then as needed for clinical assessment)

h. **Thyroid Function Test**: TSH, and free T4 tests will be performed at screening, C2D1, C3D1, C4D1 and then every 8 weeks.

i. **Antiviral Testing:** Please see exclusion criterion 17 in Section 4.3.

j. **Cardiac Assessments (obtain within 28 days of first dose): 1) ECG:** 12-lead ECG reading must be performed at screening to serve as baseline for comparison with ECG obtained for safety reason. **2) ECHO**: An ECHO must be performed at screening to serve as baseline for comparison with ECHO obtained for safety reason.

k. **Tumor Assessment:** Tumor assessments are required for all subjects within 28 days prior to enrollment. Baseline and on-treatment tumor assessments for solid tumors by iRECIST should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan and positron emission tomography (PET)/CT should be performed only if clinically indicated. Baseline and on-treatment tumor assessment for lymphoma by RECIL 2017 should be done using CT scan with contrast and PET/CT of neck, chest, abdomen, and pelvis and other known sites of disease at each time point. Please refer to Section 8 for requirements regarding disease assessment. Tumor assessments must be performed at screening and at the following intervals until disease progression is confirmed: approximately every 8 weeks through week 24 (e.g., C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 10, 13, 16, 19, 22, 25, 28 and 31), and then every 6 months (prior to cycles 37, cycle 43, etc.) up to conclusion of the study. Confirmatory scans should be performed at least 4 weeks (>28 days), but no longer than 8 weeks after initial documentation of an objective response. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, or disease progression, withdrawal of consent or death.

l. **Sparse PK, immunogenicity (i.e., ADA) and cytokine sampling (Dose Expansion Cohorts):** PK/ADA/cytokines time points for collection are outlined in supplementary PK tables in Section **6.3.1** (**Table 14 and Table 15**). Blood volumes required are provided in the SLM**. PK, ADA, cytokine samples should not**

be collected from infusion port for drug delivery i.e., recommendation is to use a separate line in the opposite arm for sample collection. If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline. If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

m. **Correlative laboratory studies**: Refer to supplementary **Table 16 for details in Section 6.3.2 plus the SLM.**
   - *Complement*
   - *Immunophenotyping and receptor occupancy*

n. **cfNA**: Collect blood prior to dosing into 2 separate cfNA Streck tubes and invert to mix thoroughly as described in SLM.

o. **SL-279252 Administration**: SL-279252 should be administered on D1, D8, and D15 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

p. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. In the event of a continuing SAE or a non-serious AE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

   - Ad hoc blood samples for clinical safety labs should be collected for AE related to IRR and/or CRS events as noted in Section 6.6.6.1 and SLM.

q. **Archival tumor tissue (from most recent biopsy)**: Provide formalin-fixed-paraffin-embedded (FFPE) tissue on slides (recommended minimum of 10 slides) or a block of FFPE tissue (the latter is preferred). Refer to Section 6.9.2.2 and the SLM for details.

r. **Tumor Biopsy**: Paired biopsies (pre- and on-treatment) obtained in subjects who have tumor accessible to core-needle biopsy. . The on-treatment biopsy should be obtained during the first cycle on or between D16-D23. On-treatment biopsies of responding or progressing lesions may be obtained for further characterization of the changes in the TME. **Please refer to Section 6.9.2.1 and SLM for details regarding biopsy**.

s. **Cycle 2 Days 15 and 16**: Collect biomarker samples outlined in **Table 16 in Section 6.3.2.** Refer to the SLM for details**.**

t. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-279252, or prior to the start of a new therapy, or at the end of study, or if the subject's participation is terminated early. See AE monitoring footnote above.

u. **Follow-Up**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (+/- 14 days) until death, withdrawal of consent or subject is lost to follow-up. Contact may include clinic visit, telephone contact, email or mail to document survival status.

6.3.1 Supplementary Tables for Schedule 1: PK, ADA, Cytokines / Dose Expansion

Table 14: Schedule 1 Dose Expansion PK, ADA, Cytokines (C1/D1 - 24 hrs post EOI)

Sample	SL-279252 PK Sampling (Expansion Cohorts) / Dosing Schedule 1 / Collect blood for PK at each time point unless otherwise specified[3]				
	C1/D1		C1/D1 and C1/D2		
	Predose	EOI	Time points relate to post EOI		
	-30 min (± 5 min)	(+ 5 min)	**2 hr** (±10 min)	**6 hr** (±30 min)	**24 hr** (± 2 hr)
PK	X[1]	X[2]	X	X	X
Cytokines	X[1]		X	X	X
ADA	X[1]				

1. Collect predose samples for ADA, PK and cytokines.
2. EOI sample should be collected within 5 minutes after stopping infusion. Date and clock time for start/stop of infusion as well as for sample collection (pre/post dose) will be recorded.
3. See the **SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**. Collect PK, ADA, cytokine sample in opposite arm rather than from infusion port for drug delivery.

Table 15: Schedule 1 Dose Expansion PK, ADA, Cytokines (C1/D15 and Beyond)

Sample	SL-279252 PK Sampling (Expansion Cohorts) / Dosing Schedule 1 / Collect blood for PK at each time point unless otherwise specified[3]								
	C1/D15, C2/D1 C3/D1 and C4/D1[4]		C1/D15 & D16, C2/D1 & D2			C3/D1 and C4/D1[4]	D1 C7, C10, C13 and C25	Collect sample for PK/ADA within 7 - 30 days post last dose of SL-279252. If this sample is positive for ADA, then monthly testing for PK/ADA required until resolution of ADA to baseline.
	Predose -30 min (± 5 min)	EOI (+ 5 min)	Time point relates to post EOI			Time point relates to post EOI	Predose[5]	
			2 hr (±10 min)	6 hr (±15 min)	24 hr (± 2 hr)	6 hr (±30 min)	-30 min (± 5 min)	
PK	X[1]	X[2]	X	X	X	X[4]	X[1]	
Cytokines (cycles 1 and 2 only)	X[1]		X[3]	X[3]	X[3]			
ADA	X[1]						X	

1. Collect predose samples for PK/ADA and cytokines. **See SLM for amount of blood needed and sample handling instructions**.
2. EOI sample should be collected within 5 minutes after stopping infusion. Date and clock time for start/stop of infusion as well as for sample collection (pre/post dose) will be recorded.
3. PK/cytokine analyses at EOI and post EOI time points indicated above on C1/D15, C1/D16, C2/D1 and C2/D2. The PK, ADA, cytokine sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA and cytokine sample collection.
4. C3/D1 and C4/D1 collect a predose sample for PK/ADA and then EOI, and 6 hr post EOI sample for PK.
5. Collect a predose sample for PK/ADA analyses on D1 of cycles 7, 10, 13, and 25. If subject has positive ADA test on D1 of cycle 13, then follow up predose PK/ ADA samples should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline.

6.3.2 Correlative Sample Time points / Schedule 1 / Dose Expansion

Table 16: Complement, Immunophenotyping Sample Time Points

Dose Expansion Cohorts	**C1/D1 & C2/D1**			**C1/D2 & C2/D2**	**C1/D5**	**C1/D8**	**C1/D15 & C2/D15**			**C1/D16 & C2/D16**
Schedule 1	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)	**96 h post EOI** (±2 hr)	**Predose** (-90 to -30 min)	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)
Complement (SC5b-9)[1]	X	X		X			X (C1D15 only)	X (C1D15 only)		X (C1D16 only)
Immunophenotyping[1]	X			X	X	X	X			X
Receptor Occupancy[1]			X						X	

1. 1. Refer to SLM for details. Complement is NOT collected on C2D15 or C2D16.

6.4 SOA Table: Schedule 2 Dose Expansion Cohorts

Dosing Schedule 2		**Once weekly (D1, D8, D15, D22) X 4 every 28 days**																		**Post Txt[s]**	**Follow Up[t]**
Cycle Length = 28 days		**Cycle 1**						**Cycle 2**						**Cycle 3**				**≥ Cycle 4**			
Procedures/ Assessments[b]	**Screen[a]**	**D1**	*D2*	**D8**	**D15**	D16	**D22**	**D1**	D2	**D8**	**D15**	D16	**D22**	**D1**	**D8**	**D15**	**D22**	**D1/ D15**	**D8/ D22**		
Study Days	**Days -21 to -1**	**1**	*2*	**8**	**15**	*16*	**22**	**29**	*30*	**36**	**43**	*44*	**50**	**57 etc.**	**64 etc.**	**71 etc.**	**78 etc.**	**85 etc.**	**99 etc.**	**w/in 30 d**	
Informed consent	X																				
Inclusion/exclusion criteria[c]	X	X																			
Demographics & medical history	X																				
Cancer treatment history	X																				
Physical examination	X	X		X	X		X	X						X				X D1 only		X	
Pulse oximetry[d]	X	X[d1]		X[d1]	X[d1]		X[d1]	X[d2]			X[d2]			X[d2]		X[d2]		X[d2]		X	
Vital signs[d]	X	X[d1]		X[d1]	X[d1]		X[d1]	X[d2]			X[d2]			X[d2]		X[d2]		X[d2]		X	
Height	X																				
Weight	X	X			X			X			X			X		X		X		X	
ECOG performance status	X	X		X	X		X	X						X				X D1 only		X	
Pregnancy test[e]	X	*Every 8 weeks*												X	*Every 8 weeks*					X	
Hematology profile[f]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	
Chemistry profile[f]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	
Ferritin		X																			
Coagulation profile[g]	X	X	X		X	X		X	X												
Thyroid test[h]	X							X						X				X[h]		X	
Antiviral testing (HBV/HCV)[i]	X																				
Cardiac:12-Lead ECG/ECHO[j]	X																				
Tumor imaging[k]	X	*Every 8 weeks through week 24 (see footnote k)*												X	*(see footnote k)*					X	X
Sparse PK/ immunogenicity/cytokine samples in Expansion cohorts[L]		X	X		X	X		X	X					X				X		X	
Complement[m]		X	X		X	X		X	X												
Immunophenotyping[m]		X	X	X	X	X		X	X		X	X									

Dosing Schedule 2		**Once weekly (D1, D8, D15, D22) X 4 every 28 days**																		**Post Txt[s]**	**Follow Up[t]**
Cycle Length = 28 days		**Cycle 1**						**Cycle 2**						**Cycle 3**				**≥ Cycle 4**			
Procedures/ Assessments[b]	**Screen[a]**	**D1**	*D2*	**D8**	**D15**	D16	**D22**	**D1**	D2	**D8**	**D15**	D16	**D22**	**D1**	**D8**	**D15**	**D22**	**D1/ D15**	**D8/ D22**		
Study Days	**Days -21 to -1**	**1**	*2*	**8**	**15**	*16*	**22**	**29**	*30*	**36**	**43**	*44*	**50**	**57 etc.**	**64 etc.**	**71 etc.**	**78 etc.**	**85 etc.**	**99 etc.**	**w/in 30 d**	
Receptor Occupancy[m]		X	X		X	X		X	X		X	X									
Cell-free nucleic acid (cfNA)[n]		X																			
SL-279252 administration[o]		X		X	X		X	X		X	X		X	X	X	X	X	X	X		
Concomitant medications	X	X	*Continuous monitoring*																	X	
AEs/SAEs[p]	X	X	*Continuous monitoring: Collect Ad hoc sample if IRR or CRS event occurs as outlined in Section 6.6.6.1 and SLM*																	X	
Archival tumor tissue[q]	X																				
Tumor biopsy[r]	X					X															
Survival																					X

Abbreviations: Txt = Treatment; w/in=within; C = Cycle; D = Day

a. **Screening:** Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-279252: hematology profile, chemistry profile, coagulation profile, pregnancy test. Baseline CT or PET/CT or MRI tumor assessments are required for all subjects within 28 days prior to enrollment. Subjects will be enrolled based on local PD-L1 tumor testing results. Any PD-L1 tumor testing results prior to enrollment are acceptable.

b. **Assessment Window:** A physical exam, weight and ECOG performance status obtained for a subject within 24 hours prior to dosing on Cycle 1, Day 1 is acceptable. With exception of Screening assessments and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window. Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

c. **Inclusion/Exclusion criteria:** Subjects must meet eligibility criteria prior to first dose of SL-279252 on C1/D1.

d. **Vital Signs:** BP, HR, T and RR must be measured after the subject has been sitting for at least five minutes. Pulse oximetry will be collected to coincide with vital sign time points noted below.

1) **Collect vital signs during Cycle 1 on Day 1, D8, D15, D22**: Predose (within 30 min of starting the infusion) and 15 min (± 5 min), 0.5 hr (± 5 min), 1 hr (±10 min), 1.5 hr (± 10 min) and 2 hr (± 10 min) **after SOI.**

2) **Collect vital signs on dosing days (Cycles ≥ 2, Days 1 and 15):** Predose (within 30 minutes of starting the infusion) and at the EOI (± 2 min)

e. **Pregnancy Test:** A serum pregnancy test (β-hCG) or urine pregnancy test must be performed at screening for all females who are of childbearing potential within 72 hrs of starting SL-279252. Repeat this test every 8 weeks during SL-279252. *Contraception should be continued for at least 30 days after the last dose of SL-279252.*

f. **Clinical Laboratory Tests (Hematology/Clinical Chemistry):** Clinical laboratory tests will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.6 for list of laboratory tests required.

g. **Coagulation Tests:** PT, INR, APTT, fibrinogen, d-dimer (the latter test at screening and then as needed for clinical assessment)

h. **Thyroid Function Test**: TSH, and free T4 tests will be performed at screening, C2D1, C3D1, C4D1 and then every 8 weeks.

i. **Antiviral Testing:** Please see exclusion criterion 17 in Section 4.3.

j. **Cardiac Assessments (obtain within 28 days of first dose): 1) ECG:** 12-lead ECG reading must be performed at screening to serve as baseline for comparison with ECG obtained for safety reason. **2) ECHO**: An ECHO must be performed at screening to serve as baseline for comparison with ECHO obtained for safety reason.

k. **Tumor Assessment:** Tumor assessments are required for all subjects within 28 days prior to enrollment. Baseline and on-treatment tumor assessments for solid tumors by iRECIST should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan and positron emission tomography (PET)/CT should be performed only if clinically indicated. Baseline and on-treatment tumor assessment for lymphoma by RECIL 2017 should be done using CT scan with contrast and PET/CT of neck, chest, abdomen, and pelvis and other known sites of disease at each time point. Please refer to Section 8 for requirements regarding disease assessment. Tumor assessments must be performed at screening and at the following intervals until disease progression is confirmed: approximately every 8 weeks through Week 24 (e.g., C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 10, 13, 16, 19, 22, 25, 28 and 31), and then every 6 months (prior to cycles 37, cycle 43, etc.) up to conclusion of the study. Confirmatory scans should be performed at least 4 weeks (>28 days), but no longer than 8 weeks after initial documentation of an objective response. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, or disease progression, withdrawal of consent or death.

l. **Sparse PK and immunogenicity (i.e., ADA) and cytokine sampling (Dose Expansion Cohorts):** PK, ADA, and cytokine time points for collection are outlined in supplementary PK **tables in Section 6.4.1 (Table 17 and Table 18).** Blood volumes required are provided in the SLM. PK, ADA, cytokine samples should not be collected from infusion port for drug delivery i.e., recommendation is to use a separate line in the opposite arm for sample collection**.** If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline. If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

m. **Correlative laboratory studies**: Refer to supplementary **Table 19 for details in Section 6.4.2 plus the SLM.**
- *Complement*
- *Immunophenotyping and receptor occupancy*

n. **cfNA**: Collect blood into 2 separate cfNA Streck tubes and invert to mix thoroughly as described in SLM.

o. **SL-279252 Administration**: SL-279252 should be administered on D1, D8, D15, and D22 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

p. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. In the event of a continuing SAE or a non-serious AE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.
- Ad hoc blood samples for clinical safety labs should be collected for AE related to IRR and/or CRS events as noted in Section 6.6.6.1.

q. **Archival tumor tissue (from most recent biopsy)**: Provide FFPE tissue on slides (recommend a minimum of 10 slides) or a block of FFPE tissue (the latter is preferred). Refer to Section 6.9.2.2 and the SLM for details.

r. **Tumor Biopsy**: Paired biopsies (pre- and on-treatment) obtained in subjects who have tumor accessible to core-needle biopsy. The on-treatment biopsy should be obtained during the first cycle on or between D16-D23. On-treatment biopsies of responding or progressing lesions may be obtained for further characterization of the changes in the TME. **Please refer to Section 6.9.2.1 and SLM for details regarding biopsy**.

s. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-279252, or prior to the start of a new therapy, or at the end of study, or if the subject's participation is terminated early. See AE monitoring footnote above.

t. **Follow-Up**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (+/- 14 days) until death, withdrawal of consent or subject is lost to follow-up. Contact may include clinic visit, telephone contact, email or mail to document survival status.

6.4.1 Supplementary Tables for Schedule 2: PK, ADA, Cytokines / Dose Expansion

Table 17: Schedule 2 Dose Expansion PK, ADA, Cytokines (C1/D1 - 24 hrs post EOI)

Sample	SL-279252 PK Sampling (Expansion Cohorts) / Dosing Schedule 2 / Collect blood for PK at each time point unless otherwise specified[3]				
	C1/D1		C1/D1 and C1/D2		
	Predose	EOI	Time points relate to post EOI		
	-30 min (± 5 min)	(+ 5 min)	**2 hr** (±10 min)	**6 hr** (±30 min)	**24 hr** (± 2 hr)
PK	X[1]	X[2]	X	X	X
Cytokines	X[1]		X	X	X
ADA	X[1]				

1. Collect predose samples for ADA, PK and cytokines.
2. EOI sample should be collected within 5 minutes after stopping infusion. Date and clock time for start/stop of infusion as well as for sample collection (pre/post dose) will be recorded.
3. See the **SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**. Collect PK, ADA, cytokine sample in opposite arm rather than from infusion port for drug delivery.

Table 18: Schedule 2 Dose Expansion PK, ADA, Cytokines (C1/D15 and Beyond)

Sample	SL-279252 PK Sampling (Expansion Cohorts) / Dosing Schedule 2 / Collect blood for PK at each time point unless otherwise specified[3]								
	C1/D15, C2/D1 C3/D1 and C4/D1[4]		C1/D15 & D16, C2/D1 & D2			C3/D1 and C4/D1[4]	D1 of C7, C10, C13 and C25	Collect sample for PK/ADA within 7 - 30 days post last dose of SL-279252. If this sample is positive for ADA, then monthly testing for PK/ADA required until resolution of ADA to baseline.
	Predose -30 min (± 5 min)	EOI (+ 5 min)	Time point relates to post EOI			Time point relates to post EOI	Predose[5]	
			2 hr (±10 min)	6 hr (±15 min)	24 hr (± 2 hr)	6 hr (±30 min)	-30 min (± 5 min)	
PK	X[1]	X[2]	X	X	X	X[4]	X[1]	
Cytokines (cycles 1 and 2 only)	X[1]		X[3]	X[3]	X[3]			
ADA	X[1]						X	

1. Collect predose samples for PK/ADA and cytokines. **See SLM for amount of blood needed and sample handling instructions**.
2. EOI sample should be collected within 5 minutes after stopping infusion. Date and clock time for start/stop of infusion as well as for sample collection (pre/post dose) will be recorded.
3. PK/cytokine analyses at EOI and post EOI time points indicated above on C1/D15, C1/D16, C2/D1 and C2/D2. The PK, ADA, cytokine sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA and cytokine sample collection.
4. C3/D1 and C4/D1 collect a predose sample for PK/ADA and then EOI, and 6 hr post EOI sample for PK.
5. Collect a predose sample for PK/ADA analyses on D1 of cycles 4, 7, 10, 13, and 25. If subject has positive ADA test on D1 of cycle 13, then follow up predose PK/ ADA samples should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline.

6.4.2 Correlative Sample Time points / Schedule 2 / Dose Expansion

Table 19: Complement, Immunophenotyping Sample Time Points

Dose Expansion Cohorts	**C1/D1 & C2/D1**			**C1/D2 & C2/D2**	**C1/D5**	**C1/D8**	**C1/D15 & C2/D15**			**C1/D16 & C2/D16**
Schedule 2	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)	**96 h post EOI** (±2 hr)	**Predose** (-90 to -30 min)	**Predose** (-90 to -30 min)	**1 hr post EOI** (±10 min)	**2 hr post EOI** (±10 min)	**24 h post EOI** (±2 hr)
Complement (SC5b-9)[1]	X	X		X			X (C1D15 only)	X (C1D15 only)		X (C1D16 only)
Immunophenotyping[1]	X			X	X	X	X			X
Receptor Occupancy[1]			X						X	

1. Refer to SLM for details. Complement is NOT collected on C2D15 or C2D16.

6.5 Demographics, Medical History, Screening and Safety Assessments

6.5.1 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed and prior to starting treatment with SL-279252. Refer to Section 13.3.

6.5.2 Eligibility Criteria

Subjects must meet all the eligibility criteria outlined in the protocol to be eligible for participation.

6.5.3 Subject Demographics

The age, sex, race, and ethnicity of each subject will be recorded during Screening.

6.5.4 Medical History

A complete medical history will be taken during the Screening period. The history will include the background and progress of the participant's malignancy and a description of prior therapies received to treat the disease under study and the response to these therapies. Documenting the response to prior PD-1/L1 inhibitor therapies is relevant to the inclusion criteria.

6.5.5 Concomitant Medications

Concomitant medications and procedures will be recorded during the Screening period and throughout the study as specified in the SOA.

6.6 Safety Evaluations

6.6.1 Physical Examination

A complete physical examination should be performed at screening and at the post-treatment visit by a qualified physician or their designee. The exam will include, at a minimum, assessments of the head and neck, eyes, ears, nose throat, skin, thyroid, cardiovascular, respiratory, gastrointestinal and neurological systems, lymph nodes and extremities. Height (at screening) and weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses. Physical exams should be performed per standard of care during the on-treatment period.

6.6.2 ECOG Performance Status

Participant's performance status will be assessed using the ECOG performance status tool (see Appendix Section 16.1).

6.6.3 Pulse Oximetry

Oxygen saturation will be measured with a pulse oximeter at room air without supplementation.

6.6.4 Vital Signs

Vital signs will be assessed in a semi-supine position at rest and will include temperature (T), systolic and diastolic blood pressure (BP), heart rate (HR), and respiratory rate (RR). BP and RR measurements should be preceded by at least 5 min of rest for the participant in a quiet setting without distractions. Refer to footnote "d" in the SOA for details on when to collect vital signs.

6.6.5 Cardiac Assessments

6.6.5.1 Electrocardiograms

A single 12-lead ECG will be obtained as outlined in the SOA using an ECG machine that automatically calculates HR and measures PR, QRS, QT, and corrected QTc (QTc) intervals. ECGs should be performed as clinically indicated during the conduct of the study. Any treatment emergent abnormalities of clinical consequence should be reported as AEs.

6.6.5.2 Echocardiogram

An ECHO will be obtained as outlined in the SOA to assess left ventricular ejection fraction. ECHOs should be performed as clinically indicated during the conduct of the study. Any treatment emergent abnormalities of clinical consequence should be reported as AEs.

6.6.6 Clinical Safety and Other Laboratory Assessments

Refer to the SOA for the timing and frequency.

<table>
<tr><th colspan="3">Clinical Safety Labs</th></tr>
<tr><th>Hematology</th><th colspan="2">Clinical Chemistry</th></tr>
<tr><td>Hemoglobin (Hgb)
Hematocrit
Platelet Count
Red Blood Cell (RBC) Count
White Blood Cell (WBC) Count
Automated WBC Differential
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td><td colspan="2">Blood urea nitrogen (BUN)
Creatinine
Glucose
Sodium
Potassium
Calcium
C reactive protein (CRP)
Liver Panel
Total and direct bilirubin
Alanine aminotransferase (ALT)
Magnesium
Phosphorus
Total Protein
Albumin
Lactate dehydrogenase
Bicarbonate (CO_2)
Ferritin (C1D1 only)
Aspartate aminotransferase (AST)
Alkaline phosphatase</td></tr>
<tr><th>Coagulation</th><th>Thyroid</th><th>Serum/Urine Pregnancy Test</th></tr>
<tr><td>Prothrombin time (PT) and International-normalized ratio (INR)
Activated partial thromboplastin time (aPTT)
Fibrinogen
D-Dimer</td><td>Thyroid stimulating hormone (TSH)
Free thyroxine 4 (T4)</td><td>β-human chorionic gonadotropin (β-hCG)</td></tr>
<tr><th>Immunogenicity Test[a]</th><th>Complement</th><th>Antiviral Testing</th></tr>
<tr><td>Anti-drug antibodies (ADA)</td><td>SC5b-9 test</td><td>Hepatitis B: HBsAg / HBV core Ab
Hepatitis C: HCV Ab / HCV RNA viral load</td></tr>
<tr><th colspan="3">Additional Laboratory Tests[a]</th></tr>
<tr><td colspan="3">cfNA (Dose Expansion Cohorts only)</td></tr>
<tr><th colspan="3">Cytokines and Chemokines Panel[a]</th></tr>
<tr><td colspan="3">Including but not limited to GM-CSF, G-CSF, tissue growth factor (TGF)-alpha, IFN-gamma, etc. See SLM for details</td></tr>
<tr><th colspan="3">Flow Cytometry Panels[a]</th></tr>
<tr><td colspan="3">Receptor Occupancy Panel
Immunophenotyping Panel
Memory Panel and Treg Panel: See SLM for details</td></tr>
</table>

a) Refer to the SLM for details for sample collection, handling, storage and shipment instructions.

6.6.6.1 Ad Hoc Labs for AEs of IRR and/or CRS

Ad hoc labs should be collected as noted if IRR and/or CRS occur. The samples to be collected are provided below.

CBC and differential **Complement (SC5b-9)** **CRP** **Ferritin** **PK, ADA** **Flow Cytometry** • **Cytokines and Chemokines Panel** • **Immunophenotyping Panel**

a) Refer to the SLM for sample collection, handling, storage and shipment instructions. PK will be measured with each corresponding ADA sample.
b) Specific biomarker, PK, ADA, and clinical samples will be collected as soon as possible if AE related to CRS and/or IRR to SL-279252 occurs.

All protocol-required laboratory assessments must be conducted in accordance with the SLM.

6.6.6.2 Pregnancy Testing

All FCBP subjects must have a negative pregnancy test (serum or urine) at Screening. A separate assessment is required if a negative Screening pregnancy test is obtained more than 72 hours before the first dose of SL-279252. Subjects with a positive pregnancy test must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described in Appendix Section 16.2.

In the rare event that β-hCG is elevated as a tumor marker, please see guidance in Appendix Section 16.2.1.

6.7 Pharmacokinetics

6.7.1 Intensive PK Sampling in Dose Escalation (Schedule 1 or Schedule 2)

Intensive serial PK samples will be collected for all subjects enrolled in dose escalation cohorts. In the first cycle starting on Day 1, samples will be collected pre-dose, at the EOI, and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours post EOI. Additional PK samples will be collected at 48, 72, and 96 hours post EOI. Actual dose administration and PK sampling times will be documented in the subject's medical record. Sample collection out to 96 hours post EOI may be truncated during dose finding based on emerging data (e.g., lower doses may require collection of PKs only through the 48-hour time point following the first infusion). Subsequently, pre-dose, EOI, 2-hour, 6-hour and 24-hour post EOI samples will be obtained on C1D15/D16 and C2D1/D2. On C3/D1 and C4/D1, a pre-dose, EOI, and 6-hour post EOI sample will be collected. Beyond cycle 4, only pre-dose samples will be collected for ADA and PK analyses on D1 of C7, C10, C13 and C25. A final PK/ADA sample should be collected within 7 – 30 days after permanently stopping treatment with SL-279252.

Refer to supplementary tables provided in Sections 6.1.1 and 6.2.1 for details.

6.7.2 Sparse PK Sampling in Dose Expansion (Schedule 1 or Schedule 2)

Sparse PK samples will be collected for all subjects enrolled in Expansion Cohorts. Actual dose administration and PK sampling times will be documented in the subject's medical record. A sample will be collected pre-dose, at the EOI and then 2 and 6 hours after the infusion on C1/D1. A 24-hour post EOI sample will be collected on Day 2 of the first cycle (C1/D2). Subsequently, pre-dose, EOI, 2-hour, 6-hour, and 24-hour post EOI samples will be obtained on C1D15/D16 and C2D1/D2. A predose, EOI and 6-hour post EOI sample will be collected on C3/D1 and cycle 4/D1. Beyond cycle 4, only pre-dose samples will be collected for ADA and PK analyses on D1 of C7, C10, C13 and C25. A final PK/ADA sample should be collected within 7 – 30 days after permanently stopping treatment with SL-79252.

Refer to supplementary tables provided in Sections 6.3.1 and 6.4.1. for details.

6.7.3 Pharmacokinetic Endpoints

The Pharmacokinetics of SL-279252 will be described using the PK parameters listed in Table 20.

Table 20: Serum SL-279252 PK Parameters

C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
$AUC_{0\text{-}last}$	The area under the serum concentration time curve, from time 0 to the last quantifiable concentration, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
$AUC_{0\text{-}t}$	The area under the serum concentration time curve, from time 0 to time=t, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
$AUC_{0\text{-}inf}$	Area under the serum concentration time curve from time 0 extrapolated to infinity, calculated as $AUC_{last} + C_{last}$/terminal elimination rate constant (λ_z). Reliability of $AUC_{0\text{-}inf}$ values is contingent on the percent of the total area obtained by extrapolation: $AUC_{0\text{-}inf}$ values with <20% of the total area coming from C_{last}/λ_z are considered acceptable. Any exceptions to the above procedures will be clearly documented/justified in the PK report.
AUC_{tau}	The area under the serum concentration time curve, over the dosing interval following doses > first dose, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from T_{last} to infinity
$t_{½}$	Terminal elimination half-life, estimated using the equation $[\ln(2)/\lambda_z]$
CL	Clearance; calculated as Dose/$AUC_{0\text{-}inf}$
V_z	Volume of distribution; calculated as Dose/(λ_z * $AUC_{0\text{-}inf}$)

6.8 Anti-drug Antibody Assessments

Pre-dose blood samples will be collected from all subjects enrolled in the study (Dose Escalation and Dose Expansion Cohorts) for determination of ADA prior to the first dose, on C1D15, and on

the first day of cycles 2, 3, 4, 7, 10, 13 and 25 and within 7-30 days of the last dose of SL-279252. The following endpoints will be calculated for each subject:

- ADA titer and status (positive, negative, inconclusive) at each timepoint
- ADA onset
- ADA duration
- Persistent vs. transient ADA

6.9 Pharmacodynamic/Biomarker Assessments

Blood samples and tumor tissue (where available) will be collected from all subjects in this study for pharmacodynamic/biomarker research as specified in the SOA for the appropriate dosing schedule (Schedule 1 or Schedule 2). Below is an overview of the Pharmacodynamic/Biomarker plan, the sample requirements, supporting analytics, and intended goal of performing the proposed assays. A separate SLM detailing the preparation, storage, and shipping requirements for blood or fresh and archival tumor tissue collection during the study will be provided.

6.9.1 Pharmacodynamic Assessments in Blood

6.9.1.1 Cytokine and Chemokine Analysis

The levels of serum proteins such as cytokines and chemokines will be measured as noted in Section 6.6.6. Levels of serum cytokines/chemokines may provide context to AEs observed in subjects following infusion of SL-279252 and may act as pharmacodynamic markers of activity. Serum cytokines will be measured for SL-279252 in dose escalation and dose expansion cohorts.

6.9.1.2 Peripheral Blood Mononuclear Cells for Receptor Occupancy

Receptor occupancy of SL-279252 on PD-L1 and OX40 will be measured by flow cytometry. This analysis will provide evidence that SL-279252 is engaging its expected targets and allow receptor occupancy (free and total) to be calculated and assessed across dose groups. Samples for receptor occupancy will be collected during dose escalation and dose expansion.

6.9.1.3 PBMC for Immunophenotyping

Protein expression of phenotypic markers, proliferation markers, and activation markers will be assessed by flow cytometry. The composition of T cells in the peripheral blood may provide insights into the mechanism of action of SL-279252 and serve as biomarkers for immune response. Samples for immunophenotyping will be collected during dose escalation and in dose expansion.

6.9.1.4 Cell-free Nucleic Acids for Exome Sequencing and TMB

Cell-free nucleic acids (cfNA) samples will only be collected in subjects in Dose Expansion Cohorts. These samples may be utilized for exome sequencing and TMB analyses. Assessing mutations (including point, insertions/deletions, etc.) in the coding sequence of nucleic acids isolated from nucleic acids shed by tumor cells into the peripheral blood or in the actual tumor environment will allow for evaluation of the mutational load, which can be correlated with subject response. Additionally, exome sequencing can provide insights into other genetic

pathways/mechanisms associated with either response or resistance to SL-279252 (e.g., mutations in antigen presentation).

6.9.2 Pharmacodynamic Assessment of Tumor Tissue

6.9.2.1 Fresh Tumor Biopsies

The efficacy of cancer immunotherapy is conditioned by the infiltration of tumors by activated tumor-specific T cells. The activity of these T cells will be affected by the immunosuppressive environment in the tumor (e.g., T-regulatory cells, and suppressive myeloid cells such as myeloid-derived suppressor cells and M2 macrophages). Therefore, the direct evaluation of the "immune landscape" inside the tumor is of great value for understanding the mechanism of action of SL-279252 and optimizing cancer immunotherapy. Immunohistochemistry (IHC) analyses and exome sequencing will be performed on the fresh tumor samples. The immune infiltrate of the tumor will be assessed by visualizing and assessing the phenotype of cells in the tumor micro-environment by IHC. Additionally, the spatial distribution and redistribution upon treatment of immune cells within the TME has also been found to be linked to the response to immunotherapies and can be evaluated by these procedures. The immune profile of the tumor could be used to predict clinical response or validate the mechanism of the immune response to SL-279252. Exome sequencing analysis will be used to detect mutations in genes associated with mechanisms of resistance (e.g., defects in antigen presentation) or response. Additional DNA/RNA analyses may be performed. For these reasons, core needle biopsies are highly recommended in subjects with tumors accessible for biopsy enrolled in the Dose Escalation or Expansion Cohorts. Three cores at each biopsy time point should be obtained for research studies (see SLM for details).

Paired biopsies are requested at Screening/Baseline (to evaluate the immune status of the tumor before SL-279252 treatment), and at Week 3 in the first treatment cycle at any time between Days 16-23, (at the expected time of an immune response to SL-279252 therapy). If the baseline biopsy is non-evaluable, the Sponsor will inform the investigator that the follow-up on-treatment biopsy can be omitted. The time interval for the second biopsy may be changed by the Sponsor if pharmacodynamic data from the Dose Escalation indicates a different time point would be more suitable.

It is strongly recommended that the biopsies are obtained from non-target and measurable lesions. If such a lesion is not present, a biopsy may be obtained from a target lesion that is 2 centimeters (cm) or more. The same lesion should be biopsied at both Screening and subsequent time points, and measurement of the lesion that is biopsied should be documented. Where possible, lymph node biopsies should be avoided (except for lymphoma subjects) as reliable measure of tumor infiltrating lymphocytes (or their activation) in a background of (non-tumor) lymphoid tissue is challenging.

If feasible, biopsy material should be collected after disease progression has been confirmed and documented, ideally on lesions that have progressed.

Priority for fresh biopsy tissue analysis based on tissue availability is IHC (including central confirmation of PD-L1 tumor testing) > exome sequencing if cfNA is non-evaluable > additional

DNA and/or RNA analyses. Samples collected on treatment or at the time of progression will be compared with baseline results.

Biopsy Collection Safety Considerations and Procedure
Three tissue cores per subject should be obtained at time points noted in the SOA. Further details are provided in the SLM.

Only percutaneous biopsies will be performed on subjects with solid tumors. Mediastinal, open surgical or laparoscopic, gastrointestinal, peritoneal or bronchial endoscopic biopsies are permitted ONLY when obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial. No laparoscopic, or endoscopic or open surgical procedure will be performed solely to obtain a biopsy for this protocol. However, excisional biopsy or endoscopic biopsy is allowed if medically-indicated and can be used for analysis. Biopsies will be sent for analyses as defined in the protocol.

Contraindications to percutaneous biopsy:

- Significant coagulopathy or anticoagulation treatment that cannot be adequately corrected.
- Severely compromised cardiopulmonary function or hemodynamic instability.
- Lack of a safe pathway to the lesion.
- Inability of the subject to cooperate with, or to be positioned for, the procedure.

If a site is deemed appropriate for biopsy with minimal risk (no more than 2% risk of serious complication requiring hospitalization) to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy should be made.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be performed only if they are of low risk (<2% major complication rate) to the participant as determined by the investigators and Interventional Radiologist.

6.9.2.2 Archival Tumor

TMB analysis may be performed on archival tumor tissue. Archival tumor tissue (1 block preferred or a minimum of 10 unstained slides of FFPE tissue; see SLM for details) that is representative of current disease status (e.g., metastatic disease) is requested in Dose Escalation and Dose Expansion Cohorts. If an inadequate amount of archived tissue is available, the subject may still participate in the study if they meet eligibility criteria for the study. Archival tissue may be accepted as a pre-treatment specimen in lieu of a fresh biopsy if the subject has not undergone treatment since time of specimen collection and if the sample was collected via core needle biopsy.

Priority for archival tissue analysis based on tissue availability is IHC > TMB* > additional DNA and/or RNA analyses. Samples collected on treatment or at the time of progression will be compared with baseline results.

***NOTE**: Preferred source for TMB analysis is cfNA; however, if cfNA is inadequate for analysis the archived tumor tissue will be used.

6.10 Assessment of Anti-tumor Activity

Anti-tumor activity will be assessed in solid tumors according to iRECIST, and in lymphoma according to RECIL 2017. Treatment beyond progression is permitted provided the subject meets protocol specified criteria (see Section 8.3). Imaging studies including CT scan, FDG-PET or MRI for disease assessment will be performed at baseline and at the following intervals until disease progression is confirmed: every 8 weeks through week 24, and every 12 weeks thereafter until year 2, and every 6 months until study conclusion. Refer to Section 8 for additional details. All subjects will be followed up for survival unless they withdraw consent.

6.11 Unscheduled Visit

In the event of an unscheduled visit, the subject should undergo safety screening to include a physical exam, vital signs (HR, BP, T, and RR) and pulse oximetry. Clinical hematology and chemistry labs may be collected if considered necessary for subject assessment. The reason for the unscheduled visit should be documented in the eCRF. If the subject is experiencing an AE, they should be referred to the appropriate medical service for proper follow up of the AE(s). All AEs or SAEs reported by the subject or observed by the investigator should be documented and reported; this includes relevant medical information gathered during the unscheduled visit related to clinical assessment of AEs or SAEs (Section 7.5).

7. SAFETY ASSESSMENTS

Subjects will be followed continuously for AEs starting when a subject has signed the ICF, throughout the course of treatment and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AEs should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 90 days after the last dose of SL-279252, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. All observed or volunteered AEs (serious or non-serious) and abnormal laboratory test findings, if applicable, whether suspected to have a causal relationship to the SL-279252 or not will be recorded in the subject medical record and in the eCRF. AEs will be graded according to NCI-CTCAE v5.0. For all AEs, sufficient information will be pursued and/or obtained to permit an adequate determination of seriousness and outcome of the event (i.e., whether it should be classified as a SAE or not) and an assessment of the causal relationship between the AE and SL-279252. AEs will be followed until resolution (or return to baseline) or stabilization. Refer to Section 7.5 for documentation and reporting of AEs.

7.1 Assessment of Severity

The descriptions and grading scales found in the revised NCI-CTCAE version 5.0 will be utilized for AE reporting. A copy of these criteria can be downloaded from the website: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- **Grade 4:** Life-threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For AEs not included in the NCI-CTCAE v5.0 grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events may be potentially life-threatening or incapacitating.

NOTE: A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe.

7.2 Definitions for Safety Parameters

Event	Definition
Adverse Event (AE)	The AE observation period starts at the time of signing informed consent and includes baseline or washout periods, even if no study treatment has been administered. AE is any untoward medical occurrence in a subject to whom the IP has been administered, regardless of whether the event is considered related to that product. An AE is also an undesirable medical condition due to a study-related procedure.
Adverse Reaction (AR)	AR is an untoward and unintended response in a subject to an IP. A causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse	An AE or suspected AR that is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

Event	Definition
Event (SAE) or Serious Adverse Reaction (SAR)	• Death (**Note**: death is an outcome not an event) • A life-threatening AE (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • A congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Laboratory test(s) that meet definition of an AE or SAE:	• Any laboratory test result that meets the definition of an AE or SAE or requires holding or discontinuation of SL-279252, or requires corrective therapy, must be documented appropriately. • Ad hoc labs should be collected as noted in Section 6.6.6.1 above if AEs of IRR and/or CRS occur. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the subject's medical record and recorded in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with clinically significant abnormal values during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., AE, SAE or dose interruption), then the results must be recorded in the eCRF.
Unexpected Adverse Reaction	An adverse reaction (causality related Adverse Event), the nature, severity or outcome of which is not consistent with the reference safety information section of the product IB. Product reference safety information is contained in the current Guidance for Investigators in Section 6.0 of the Investigator's Brochure provided to the Investigator by the Sponsor.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Suspected Adverse Reaction (causality related AE) that is serious and unexpected.

7.2.1 Events not Qualifying as AEs/SAEs

The following are not considered to be AEs or SAEs:

- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is considered the AE.

- Elective procedures, planned hospitalizations, and procedures for treatment of conditions noted in the patient's medical history (present prior to signing the ICF) that have not worsened are not considered AEs.
- Situations where an untoward medical occurrence did not occur (i.e., admission to hospital for social circumstances).
- Anticipated day-to-day fluctuations of pre-existing medical conditions that were present at start of study. These conditions are considered part of the patient's medical history and must be adequately documented on the appropriate page of the CRF.
- Clear progression of disease under study should not be reported as an AE or SAE (unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular patient). Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE.
- In the case where the medical condition is known when the participant enters the trial, only worsening (increased frequency or intensity of the episodes or attacks) will be documented as an AE. If the disease is detected during the trial, and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped together in the CRF, and the diagnosis will be clearly described.
- Laboratory abnormalities: An isolated, out-of-range laboratory result in the absence of any associated, clinical finding may or may not be considered an AE; the Investigator's evaluation should be based on a consideration of the overall clinical context.

7.3 Classification of an Adverse Event

7.3.1 Assessment of Causality

The clinician's assessment of an AE's relationship to IP is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to IP assessed. In a clinical trial, the IP must always be suspect. To help assess causality, the following guidelines are used.

Related – The AE is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

Not Related – There is not a reasonable possibility that the administration of IP caused the event, there is no temporal relationship between IP and event onset, or an alternate etiology has been established.

7.3.2 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected.

- **Unexpected** - An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information section 6.0 (Guidance for

Investigators) of the IB [SL2018IB001_01] for the IP. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug not specifically mentioned as occurring with the IP under investigation.

- **Expected** - AEs that are common and known to occur for the IP being studied. Expectedness refers to the awareness of AEs previously observed, not on what might be anticipated from the properties of the IP.

7.4 Timing for Event Assessment and Follow-up

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the pre-existing condition deteriorates at any time after the subject signs the main study ICF, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

The highest grade in severity for each AE will be documented. AEs characterized as intermittent require documentation of onset and duration of each episode.

7.5 Procedures for Recording and Reporting of Adverse Events

Event	Reporting Procedures
Adverse Event	Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF, regardless of whether the event(s) is attributed to trial medication. If another anti-cancer agent is started, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, and action taken. Follow-up information should be provided as necessary. AEs will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.
Serious Adverse Event Serious	The study clinician will complete a SAE Form within the following timelines: • All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study Sponsor or designee *within 24 hours of site awareness.* • Other SAEs regardless of relationship, will be submitted to the study Sponsor or designee *within 24 hours of site awareness*. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event

Event	Reporting Procedures
Adverse Event (continued from previous page)	may be requested by the Sponsor and should be provided as soon as possible. The Sponsor will be responsible for notifying Regulatory Authorities of any unexpected fatal or life-threatening suspected AR as soon as possible *but in no case later than 7 calendar* days after the Sponsor's initial receipt of the information. The Sponsor will be responsible for notifying Regulatory Authorities of any other serious unexpected suspected adverse reaction as soon as possible *but in no case later than 15 calendar* days after the Sponsor's initial receipt of the information. **Sponsor Contact Information for SAE Reporting** **Email:** [redacted] **eFax number:** [redacted]

7.6 Reporting of Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented via the ***Pregnancy Report Form provided in the SRM***. Any pregnancy occurring in a participant or participant's partner from the time of consent to 30 days after the last dose of IP must be reported and then followed for outcome. Newborn infants born to the subject or subject's partner should be followed until 30 days old.

A FCBP must discontinue SL-279252 therapy immediately if they become pregnant during the study. To ensure subject safety, each pregnancy must be reported to the Sponsor within two weeks of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as a SAE. Spontaneous abortions must be reported as a SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has discontinued SL-279252 must be promptly reported to the Sponsor .

7.7 Reporting of Overdose

The following events should also be reported to the Sponsor and PrimeVigilance *within 24 hours*:

- Overdose: An overdose of SL-279252 should be reported within 24 hours to the Sponsor
- Suspected transmission of an infectious agent due to contamination of drug product
- Other events related to misuse of IP

7.8 Study Halting Rules

Administration of IP will be halted if a fatal SAE is reported to the Sponsor related to the SL-279252. The Sponsor will inform the investigators immediately if such an event is reported and screening and enrollment will stop accepting new study subjects. The Sponsor will convene an ad hoc meeting of the SMC to review the SAE and overall safety profile and provide

recommendations. The study Sponsor will inform the regulatory authorities (i.e., FDA, European Medicines Agency , Health Canada, etc.) of the temporary halt and the disposition of the study.

7.9 Safety Oversight

An SMC will be implemented in this study and will consist of investigators and Sponsor representatives. SMC meetings will be conducted monthly (or more frequently if required) during dose escalation provided subjects have been enrolled and data are available to be reviewed. The SMC will operate in accordance with the SMC charter which will define roles and accountabilities and the process for safety review.

Throughout the conduct of the study, safety data will be reviewed for each subject on an ongoing basis. Additionally, periodic safety reviews will be undertaken by the SMC. Based on the severity of the DLTs, indicators of potential anti-tumor activity, and other factors, a recommendation on whether to modify the dose and/or study design; or continue enrollment will be made by the Sponsor collaboratively with input from the SMC. Regulatory authorities and IRBs/IECs will be notified of any decisions to prematurely halt the study or subject enrollment. (See section 14.1 for details on safety meetings).

A safety governance board will also be formed. The remit of this board will be to conduct periodic safety reviews across all trials conducted by the Sponsor including protocol SL01-DEL-101. The safety governance board will be comprised of two physicians with pertinent expertise who are not involved in the design, conduct or analysis of SL01-DEL-101. The safety governance board will operate in accordance with a charter which will define roles and accountabilities and the process for their safety review.

8. ANTI-TUMOR ACTIVITY ASSESSMENTS

Although the clinical benefit of SL-279252 has not yet been established, the intent of offering this IP is to provide a possible therapeutic benefit, and thus the participant will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

For the purposes of this study, participants should be evaluated for response as outlined in the SOA. Confirmatory scans should be performed at least 4 weeks (>28 days), but no longer than 8 weeks after initial documentation of an objective response. All participants who receive at least 3 doses of SL-279252 and had the first disease assessment at the 8-week time point will be considered evaluable for response.

Assessments must be performed on a calendar schedule and should not be affected by dose interruptions or delays. Refer to the SOA (Section 6) for the schedule of disease assessments. More frequent disease assessments may be performed at the discretion of the investigator. For subjects whose disease may be followed by well-characterized tumor markers, disease assessments should include results of tumor marker assessments. If study treatment is withdrawn for reasons other than disease progression, radiographic disease assessments should continue as per the SOA until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death. See Sections 8.3 for criteria for continuing treatment past disease progression.

8.1 Disease Assessment for Solid Tumor Histologies

For solid tumor histologies, response and progression will be evaluated in this study using the international criteria proposed by the RECIST working group for use in trials testing immunotherapies (iRECIST) [Seymour, 2017].

The iRECIST guidelines are based on principles used in RECIST 1.1 [Eisenhauer, 2009]. The responses assigned using iRECIST have a prefix of "i" (i.e., immune) to differentiate from responses assigned using RECIST 1.1. e.g. iCR, iPR, iSD, iUPD (unconfirmed progressive disease), iCPD (confirmed progressive disease). The major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage. iRECIST defines progression based on RECIST 1.1 principles; however, progression requires confirmation. The RECIST 1.1 guidelines and iRECIST guidelines are included in this document for this reason (Section 16.6).

Screening and on-treatment disease assessments will include imaging of the chest, abdomen and pelvis (e.g., computed tomography (CT), magnetic resonance imaging (MRI), bone scan, PET/CT and/or plain radiographs). CT scan with contrast of the chest, abdomen and pelvis is the preferred method to measure lesions selected for response assessment and should be performed at screening and on-treatment. PET/CT scan cannot be substituted for lesion measurements. For subjects with known brain metastases, MRI of the brain with contrast should be performed at screening and on-treatment to assess for response or progression. Bone scans and PET/CT scans should be performed at screening and on-treatment as clinically indicated.

Screening/baseline CT or MRI tumor assessments are required for all subjects within 28 days prior to enrollment. All post-baseline assessments require imaging of disease sites identified by baseline scans. The method used to document screening disease status should be used consistently throughout the study to facilitate comparison of scan results.

If a CT scan with contrast is contraindicated (i.e., hypersensitivity reaction to contrast agent), MRI may be used as an alternative method of baseline disease assessment, except for chest CT scan. If a chest CT scan with contrast is contraindicated, a chest CT scan without contrast should be performed.

8.1.1 Assessment of Response by iRECIST – Solid Tumors

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the iRECIST criteria. Please see Appendix Section 16.6 for detailed information regarding iRECIST methodology and criteria.

8.1.2 Response and Stable Disease Duration

Response duration will be measured from the time measurement criteria for iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline). Stable disease (SD) duration will be measured from the time of start of treatment until

the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.2 Disease Assessment for Lymphomas

International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017) will be used for assessment of tumor response in participants with lymphoma [Younes, 2017].

Screening/baseline and on-treatment disease assessments will include both CT scan with contrast of the neck, chest, abdomen and pelvis and FDG-PET scan. CT scan with contrast of the neck, chest, abdomen and pelvis is the preferred method to measure lesions selected for response assessment. For subjects with known brain metastases, MRI of the brain with contrast should be performed at screening and on-treatment to assess for response or progression. Other imaging including MRI, bone scan, and/or plain radiographs will be performed as clinically indicated.

Screening/baseline MRI, CT or PET/CT tumor assessments are required for all subjects within 28 days prior to enrollment. All post-baseline assessments require imaging of disease sites identified by baseline scans. The method used to document screening disease status should be used consistently throughout the study to facilitate comparison of scan results.

If a CT scan with contrast is contraindicated (i.e., hypersensitivity reaction to contrast agent), MRI may be used as an alternative method of baseline disease assessment, except for chest CT scan. If a chest CT scan with contrast is contraindicated, a chest CT scan without contrast should be performed.

8.2.1 Assessment of Response by RECIL – Lymphomas

In participants with disseminated disease, a maximum of three target lesions should be selected and used to estimate tumor response. Please see Appendix Section 16.7 for detailed information regarding RECIL methodology and criteria.

8.3 Criteria for Treatment Beyond Initial Progression

Subjects will be permitted to continue IP beyond initial progressive disease provided the subject does not have clinical symptoms of progression, is tolerating IP, and is gaining clinical benefit as assessed by the investigator. The subject must be made aware of the potential benefits and risks of continuing the IP in the setting of progressive disease by providing a separate written informed consent.

The subject may continue to be treated until one of the following criteria is met:

- Confirmed progressive disease (defined in Appendix Section 16.6.3 for solid tumors and Appendix Section 16.7.1 for lymphomas)
- Meets any of the criteria for discontinuation of IP (see Section 3.6)
- Develops clinical symptoms or signs such that the benefit-risk ratio of continuing therapy is no longer justified
- Experiences rapid progressive disease with risk to vital organs or critical anatomical sites requiring urgent medical intervention
- Decline in ECOG PS

9. STATISTICAL CONSIDERATIONS

9.1 Description of Statistical Methods

The study has 2 parts: dose escalation and dose expansion. During dose escalation, the primary objective is to evaluate the safety and tolerability of SL-279252 and to identify the MTD or MAD of SL-279252 in participants with locally advanced or metastatic select malignancies. Schedule 1 will be evaluated first, with dose escalation following the Keyboard design with a target DLT rate of 30% (acceptable range of 25-33.3%). Ten DLs are planned with a planned maximum sample size of 42 subjects. Single subject cohorts may initially be enrolled until the subject in a single subject cohort experiences a qualifying ≥ Grade 2 toxicity (see Sections 3.2.5 and 3.2.6) or a DLT **OR** DL 6 is reached. Subsequently, cohorts of at least 3 subjects will be enrolled. The full dose escalation rules are outlined in Appendix Section 16.3. The Sponsor, in consultation with the SMC, may decide to stop enrollment in Schedule 1 early (e.g., based on safety, pharmacodynamics) and begin enrollment in Schedule 2 (see Section 3.2.7). If Schedule 2 is opened, dose escalation will also follow the Keyboard design with the same target DLT rate of 30%. We anticipate that 4 DLs will be evaluated in Schedule 2 with a planned maximum sample size of 15 subjects. All cohorts will enroll at least 3 subjects in Schedule 2 (see full dose escalation rules in Appendix Section 16.3). **NOTE:** 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. If both schedules are evaluated, the MTD or MAD may be determined for each schedule (denoted MTD1/MAD1 and MTD2/MAD2). The MTD(s) will be determined using isotonic regression based on DLTs observed during dose escalation (see Section 9.2.1). A MAD will be reported if a schedule is fully evaluated, but the DLT rate never reaches the target range of 25-33.3%.

During the dose escalation additional subjects (approximately 6) may be enrolled into a pharmacodynamic cohort to obtain additional pharmacodynamic data at select dose levels that have previously completed evaluation for safety and not exceeded the MTD.

After dose escalation, up to 2 expansion cohorts (n=up to 15 subjects each) may be enrolled to further explore up to 2 different doses. The Sponsor, in consultation with the SMC, will determine the dose(s) and schedule to be evaluated during dose expansion based on the totality of data in the dose escalation cohorts. The primary objective during dose expansion is to further characterize the safety of SL-279252. Special attention will be paid to IRRs and toxicities that require discontinuation of SL-279252. See Section 9.2.2 for details on the continuous toxicity monitoring that will be implemented across the expansion cohorts. The tumor types for dose expansion will be determined after review of data collected during dose escalation. The RP2D will be determined after review of data collected during both dose escalation and dose expansion and will take safety (including delayed toxicities that do not occur during the DLT period), pharmacodynamics, PK, and efficacy into account. The RP2D will not exceed the MTD.

9.2 Sample Size and Statistical Hypotheses

9.2.1 Dose Escalation

The planned sample size for the dose escalation part of the study is 63 subjects. For Schedule 1, the maximum planned sample size for dose escalation will be 42 subjects, and for Schedule 2, the

maximum planned sample size for dose escalation will be 15 subjects. The planned number of subjects to obtain additional pharmacodynamic data at select dose levels is approximately 6 subjects.

These sample sizes for dose escalation were chosen based on simulation results demonstrating good operating characteristics (see tables below) with these sample sizes using the Keyboard design (see dose escalation rules in Appendix Section 16.3). **NOTE:** The maximum planned sample sizes may be revised if additional DLs are evaluated or if more subjects (i.e., subjects available for dosing beyond the number required in a cohort) are enrolled than anticipated. The Sponsor, in consultation with the SMC, may also elect to add subjects if additional safety data are needed to select a dose and schedule for the expansion cohorts. Six (6) subjects must be treated at a dose level to confirm safety and tolerability before a dose can be used in an expansion cohort.

All simulation results are based on 5000 simulations and assume the following:

- The target DLT rate is 30% (acceptable range of 25-33.3%)
- Dose escalation will stop early if 12 subjects are enrolled at the same DL (See Scenarios 1 and 3 in Appendix Section 16.3)
- If there is more than a 95% chance that the current dose is above the MTD, that dose and higher doses will be eliminated from the trial to prevent exposing future subjects to overly toxic doses

9.2.1.1 Simulations for Schedule 1 (assuming 10 dose levels)

The first set of simulations assume the following:

- Subjects are enrolled in cohorts of 3 (i.e., dose escalation decisions are made after the 3 subjects in a cohort are evaluated)
- Maximum sample size = 42

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Number of Subjects	% Early Stopping
Scenario 1												
True DLT rate	0.12	0.3	0.46	0.48	0.5	0.52	0.54	0.56	0.58	0.6		
Selection %	22.64	57.7	15.24	3.26	0.52	0.08	0	0	0	0		0.56
# Subjects treated	6.52	8.95	4.24	0.99	0.21	0.03	0	0	0	0	20.9	
Scenario 2												
True DLT rate	0.05	0.11	0.3	0.46	0.48	0.5	0.52	0.54	0.56	0.58		
Selection %	1.1	22.2	57.72	15.2	3.1	0.58	0.06	0.02	0	0		0.02
# Subjects treated	3.72	6.38	9.02	4.16	0.95	0.21	0.03	0	0	0	24.5	
Scenario 3												
True DLT rate	0.04	0.08	0.18	0.3	0.42	0.47	0.5	0.56	0.58	0.65		
Selection %	0.5	5.32	30.5	42.16	17.14	3.62	0.64	0.08	0.04	0		0
# Subjects treated	3.49	4.55	7	7.3	3.87	1.14	0.22	0.03	0.01	0	27.6	
Scenario 4												
True DLT rate	0.02	0.06	0.09	0.15	0.3	0.43	0.46	0.51	0.55	0.59		
Selection %	0.14	1.34	4.32	25.62	47.86	16.04	3.84	0.8	0.04	0		0
# Subjects treated	3.24	3.76	4.39	6.56	7.87	3.95	1.05	0.21	0.03	0	31.1	
Scenario 5												
True DLT rate	0.04	0.07	0.1	0.13	0.15	0.3	0.42	0.48	0.53	0.58		
Selection %	0.36	1.6	4.3	7.58	23.4	41.36	16.86	3.7	0.64	0.14		0.06
# Subjects treated	3.42	3.94	4.4	4.7	6	6.99	3.6	0.86	0.14	0.02	34.1	

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Number of Subjects	% Early Stopping
Scenario 6												
True DLT rate	0.04	0.06	0.09	0.11	0.13	0.15	0.3	0.47	0.54	0.6		
Selection %	0.4	1.18	3.34	5.38	7.08	21.98	45.48	12.84	2.02	0.28		0.02
# Subjects treated	3.45	3.78	4.18	4.43	4.5	5.69	6.7	2.95	0.47	0.06	36.2	
Scenario 7												
True DLT rate	0.04	0.06	0.08	0.1	0.12	0.13	0.16	0.3	0.48	0.68		
Selection %	0.34	0.92	2.28	4.76	5.12	7.52	22.16	41.88	14.28	0.7		0.04
# Subjects treated	3.46	3.73	3.97	4.29	4.35	4.42	5.35	5.7	2.38	0.28	37.9	
Scenario 8												
True DLT rate	0.02	0.03	0.05	0.06	0.08	0.09	0.11	0.12	0.3	0.45		
Selection %	0.02	0.1	0.54	1.12	2.7	2.78	5.28	20.52	47.78	19.14		0.02
# Subjects treated	3.19	3.33	3.53	3.7	3.99	4.03	4.23	5.29	6.11	2.73	40.1	
Scenario 9												
True DLT rate	0.02	0.04	0.06	0.08	0.09	0.1	0.12	0.14	0.15	0.3		
Selection %	0.06	0.38	1.06	2.52	3.04	3.92	6.24	9.88	25.28	47.6		0.02
# Subjects treated	3.21	3.44	3.71	3.96	4.06	4.12	4.31	4.2	4.15	4.58	39.7	

The second set of simulations assume the following:

- Subjects are enrolled in cohorts of 1 (i.e., dose escalation decisions are made after each subject is evaluated)
- Maximum sample size = 42

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Number of Subjects	% Early Stopping
Scenario 1												
True DLT rate	0.12	0.3	0.46	0.48	0.5	0.52	0.54	0.56	0.58	0.6		
Selection %	21.86	54.32	15.96	4.24	1.72	0.68	0.26	0.1	0.02	0		0.84
# Subjects treated	5.67	8.49	4.67	1.95	0.95	0.47	0.22	0.1	0.03	0.01	22.6	
Scenario 2												
True DLT rate	0.05	0.11	0.3	0.46	0.48	0.5	0.52	0.54	0.56	0.58		
Selection %	1.02	20.74	54.62	15.02	5.04	2.28	0.86	0.26	0.06	0.06		0.04
# Subjects treated	1.88	5.51	8.42	4.61	2.08	1.06	0.52	0.24	0.1	0.04	24.4	
Scenario 3												
True DLT rate	0.04	0.08	0.18	0.3	0.42	0.47	0.5	0.56	0.58	0.65		
Selection %	0.28	4.24	26.08	41.24	18.4	6.32	2.56	0.62	0.2	0.02		0.04
# Subjects treated	1.49	2.77	5.74	7.15	4.65	2.26	1.15	0.51	0.2	0.07	26	
Scenario 4												
True DLT rate	0.02	0.06	0.09	0.15	0.3	0.43	0.46	0.51	0.55	0.59		
Selection %	0.14	0.7	2.7	23.94	45.2	17.72	6.56	2.28	0.56	0.2		0
# Subjects treated	1.28	1.65	2.46	5.6	7.57	4.62	2.32	1.11	0.46	0.18	27.3	
Scenario 5												
True DLT rate	0.04	0.07	0.1	0.13	0.15	0.3	0.42	0.48	0.53	0.58		
Selection %	0.24	0.98	2.86	5	21.28	43.58	18.16	5.86	1.64	0.38		0.02
# Subjects treated	1.43	1.77	2.22	2.67	5.25	7.19	4.49	2.14	0.92	0.39	28.5	
Scenario 6												
True DLT rate	0.04	0.06	0.09	0.11	0.13	0.15	0.3	0.47	0.54	0.6		
Selection %	0.26	0.72	1.82	2.8	5.04	22.68	48.78	14.68	2.72	0.5		0
# Subjects treated	1.4	1.64	1.9	2.2	2.72	5.38	7.64	4.25	1.57	0.57	29.3	

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Number of Subjects	% Early Stopping
Scenario 7												
True DLT rate	0.04	0.06	0.08	0.1	0.12	0.13	0.16	0.3	0.48	0.68		
Selection %	0.2	0.68	1.24	2.16	3.58	5.68	24.1	48.32	13.82	0.22		0
# Subjects treated	1.36	1.58	1.82	2.06	2.37	2.82	5.4	7.52	4.17	1.08	30.2	
Scenario 8												
True DLT rate	0.02	0.03	0.05	0.06	0.08	0.09	0.11	0.12	0.3	0.45		
Selection %	0.06	0.04	0.36	0.62	1.06	1.86	2.98	21.12	53.16	18.74		0
# Subjects treated	1.17	1.25	1.44	1.59	1.77	2.01	2.34	5.39	8.21	4.91	30.1	
Scenario 9												
True DLT rate	0.02	0.04	0.06	0.08	0.09	0.1	0.12	0.14	0.15	0.3		
Selection %	0.08	0.24	0.5	1.04	1.54	2.18	3.66	5.68	22.98	62.1		0
# Subjects treated	1.2	1.37	1.58	1.77	1.89	2.04	2.29	2.71	5.38	8.53	28.8	

For Schedule 1, with a maximum of 42 subjects, the chance of selecting the true MTD is at least 40% for a range of possible scenarios. With single subject cohorts to start, followed by 3 subject cohorts, results will likely be somewhere in between the 2 sets of simulations provided, but should still provide at least 40% precision in selecting the MTD.

9.2.1.2 Simulations for Schedule 2 (assuming 4 dose levels)

The simulations assume the following:

- Subjects are enrolled in cohorts of 3 (i.e., dose escalation decisions are made after each subject is evaluated)
- Maximum sample size = 15

	Dose 1	Dose 2	Dose 3	Dose 4	Number of Subjects	% Early Stopping
Scenario 1						
True DLT rate	0.3	0.47	0.55	0.64		
Selection %	64.36	18.02	4.06	0.26		13.3
# subjects treated	8.84	3.62	0.56	0.04	13.1	
Scenario 2						
True DLT rate	0.11	0.3	0.45	0.67		
Selection %	23.82	49.9	24.04	1.94		0.3
# subjects treated	5.66	6.44	2.48	0.28	14.9	
Scenario 3						
True DLT rate	0.02	0.13	0.3	0.47		
Selection %	1.18	24.46	54.24	20.12		0
# subjects treated	3.42	5.23	4.83	1.51	15	
Scenario 4						
True DLT rate	0.05	0.1	0.15	0.3		
Selection %	1.34	8.58	38.22	51.84		0.02
# subjects treated	3.66	4.25	4.15	2.93	15	

For Schedule 2, with a maximum of 15 subjects, the chance of selecting the true MTD is at least 40% for a range of possible scenarios. Only 3 subject cohorts were considered for Schedule 2.

If both Schedule 1 and 2 are evaluated, the planned maximum total sample size during dose escalation process is 57 subjects. If only Schedule 1 is evaluated (which is expected), the planned maximum total sample size during dose escalation is 42 subjects. The final sample size will depend on whether dose escalation is stopped early (as outlined in Appendix Section 16.3), whether 1 or 2 schedules are evaluated, and whether any revisions are needed to the maximum sample sizes.

9.2.2 Dose Expansion Cohorts

Up to 2 expansion cohorts may be enrolled to further explore the safety of SL-279252. Enrolling up to 15 subjects in each expansion cohort will allow further characterization of the safety profile of up to 2 doses of SL-279252, with particular emphasis on IRRs and toxicities leading to discontinuation of SL-279252. Specifically, continuous toxicity monitoring (using sequential boundaries) will be used within each cohort.

Accrual will be temporarily stopped if excessive numbers of ≥ Grade 3 IRRs are observed (i.e., if b_n 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 Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary, b_n	-	-	-	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 b_n 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 Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary, b_n	-	-	3	3	4	4	4	4	5	5	5	6	6	6	6

9.3 Populations for Analyses

For the analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the main study ICF.
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 All Treated population who receive at least 2 doses of SL-279252 for Schedule 1 or at least 3 doses for Schedule 2, 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. Evaluable subjects will be used to guide dose escalation and to determine the MTD or MAD.
Evaluable for Efficacy	A subject who received at least 3 doses of SL-279252 and had at least one post-baseline disease assessment or had progressed or died before the first post-baseline disease assessment. .
Pharmacokinetic	All subjects in the All Treated population who received at least one dose of SL-279252 and have at least one evaluable post-dose sample collected. The PK population will be used for PK analysis.
Pharmacodynamic	All subjects in the All Treated population for whom sufficient samples are available for the analysis. The pharmacodynamic population will be used for the pharmacodynamic data analysis.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary outcome measures. The planned statistical analyses for pharmacokinetic and specific pharmacodynamic markers that will be utilized in dose selection will also be summarized. Other biomarker exploratory analyses will be described in the SAP finalized before database lock.

9.4.1 Analysis of the Primary Outcome Measures

9.4.1.1 Dose Escalation

During dose escalation, DLTs will be tabulated for evaluable subjects by dose level within each schedule. For single subject cohorts, qualifying ≥ Grade 2 toxicities that trigger a change to at least 3 subject cohorts will also be tabulated. Frequency tables will be used to describe safety and tolerability parameters such as: AEs, irAEs, SAEs, fatal SAEs and irAEs leading to discontinuation of SL-279252. Tables will be presented for the whole population, and within each dose level separately. Changes in safety assessments (e.g., laboratory parameters, etc.) will also be summarized using descriptive statistics. These will also be presented for the whole population, and

within each dose level separately. Graphs may also be presented where appropriate. The All Treated population will be used for these analyses.

The MAD will be reported, or the MTD will be estimated using isotonic regression (based on the DLTs observed in evaluable subjects). A MAD will be reported if a schedule is fully evaluated, but the DLT rate never reaches the target range of 25-33.3%. Otherwise, an MTD will be reported. Isotonic regression is a way to estimate the MTD under the assumption that toxicity increases with dose. Specifically, the MTD is selected as the dose for which the isotonic estimate of the DLT rate is closest to the target DLT rate of 0.3. If there are ties, we select the highest dose level when the isotonic estimate is lower than the target DLT rate; and we select the lowest dose level when the isotonic estimate is greater than the target DLT rate. 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. The Evaluable for Dose Escalation population will be used for these analyses. **NOTE:** 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.

9.4.1.2 Dose Expansion

During dose expansion, frequency tables will be used to describe safety and tolerability parameters such as: AEs, irAEs, SAEs, fatal SAEs and irAEs leading to discontinuation of SL-279252. Summaries will be presented within each cohort separately. Changes in safety assessments (e.g., laboratory parameters etc.) will also be summarized using descriptive statistics. These will also be presented within each cohort separately. Graphs may also be presented where appropriate. The All Treated population will be used for these analyses.

Continuous toxicity monitoring will be used to specifically monitor IRRs and toxicities leading to discontinuation of SL-279252 as described in Section 9.2.2.

9.4.2 Analysis of the Secondary Outcome Measures

ORR and CBR will be estimated and reported along with exact 95% confidence intervals. Efficacy will be evaluated within each expansion cohort separately. Efficacy will be summarized by dose level during dose escalation and will be summarized across dose levels and across the study as a whole as appropriate. iRECIST will be the disease assessment tool for solid tumors and RECIL 2017 will be the disease assessment tool for lymphoma.

The RP2D will be selected after review of all the data collected during dose escalation and expansion and will take safety (including delayed toxicities that do not occur during the DLT period), pharmacodynamics and efficacy into account. The RP2D will not exceed the MTD or MAD.

9.4.3 Exploratory Analyses

Descriptive statistics will be used to summarize changes from baseline in plasma cytokine levels, cell counts and percentages of circulating immune cells. Complement activation by assessment of SC5b-9 terminal fragment and immune cell activation state will also be evaluated. During dose escalation and expansion, receptor occupancy (free and total) of SL-279252 on PD-L1 and OX40 will be measured by flow cytometry and will be assessed within each dose level separately. During dose expansion, cfNA samples will be evaluated for analysis for TMB and exome sequencing. Associations between biomarkers and efficacy outcomes may be explored as appropriate.

If paired biopsies are collected in subjects from the dose escalation or expansion cohorts, they will be evaluated for changes in the TME pre-and post-treatment. Additional details will be provided in the SAP.

Each subject will be followed for progression-free survival and overall survival, and this information will be presented graphically using swimmer plots or Kaplan-Meier plots. If appropriate, TTR, DOR, progression-free survival and overall survival may also be summarized using the Kaplan-Meier method, with medians reported along with 95% confidence intervals.

9.5 Pharmacokinetic Analyses

9.5.1 Pharmacokinetic Populations

The PK population is defined as all subjects in the All Treated population who received at least one dose of SL-279252 and have at least one evaluable post-dose PK sample collected.

All PK analyses and reporting will be performed according to applicable Standard Operating Procedures and protocol specifications. Programming of tables, figures, and listings will be performed using R version 3.4.0 or later (R Foundation for Statistical Computing, Vienna, Austria). PK parameters will be calculated using Phoenix® WinNonlin® 6.3 or later software ([redacted]) using actual sampling times. If actual sampling times are not available, nominal sampling times will be used.

Individual serum concentrations will be listed by nominal times. Summaries of serum concentration data will include data for all subjects who receive at least one dose of SL-279252 and have at least one evaluable serum sample. Table summaries of serum concentrations will be displayed versus nominal times. Figures of individual subject drug concentrations versus actual sampling times will be presented on linear and semi-logarithmic scales by dose and schedule, as appropriate. Figures of summarized drug concentrations versus nominal sampling times will be presented on linear and semi-logarithmic scales by dose, as appropriate. PK parameters for SL-279252 will be calculated as described in Table 20. Additional parameters may be calculated as necessary.

PK parameters will be calculated using non-compartmental methods for subjects with sufficient data to estimate the parameters. PK parameters will be listed for each individual subject and summarized by cohort, dose and schedule, as appropriate. The following descriptive statistics will be provided: n (number of subjects with non-missing data), arithmetic mean (mean), standard deviation, standard error, arithmetic coefficient of variation (CV%), median, minimum, and maximum. Geometric mean (geomean), geometric mean CV%, lower 95% confidence interval around the geometric mean (95% confidence interval lower geomean), and upper 95% confidence interval around the geometric mean (95% confidence interval upper geomean) will be calculated. T_{max} and T_{last} will be presented as median, minimum and maximum.

9.5.2 Exploratory Exposure-Response Analyses

Exploratory exposure-response and exposure-safety relationships may be performed by various methods that may include population PK/pharmacodynamic analysis. Exposure-response analysis may be explored by evaluating potential relationships between exposure and efficacy and/or safety parameters such as incidence of ADA and AEs, receptor occupancy, cytokines, lymphocytes, and response rates.

9.6 Anti-Drug Antibody Analysis

Individual subject ADA titer and status (positive, negative, inconclusive) vs. nominal time will be reported and summarized by dose level during dose escalation and during dose expansion. Onset and duration of ADA by subject, characterization of subjects as having a persistent or transient ADA response will also be summarized by dose level during dose escalation and dose expansion. ADA isotype may be reported, if supported by the data. Descriptive statistics, including 95% confidence intervals where appropriate, will be reported for each endpoint.

10. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Sponsor or its designees
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits will be conducted by the Sponsor or designee of the Sponsor to ensure GCP and monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA AND DOCUMENTS

11.1 Source Data

Source documents are where data are first recorded, and from which subjects' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

11.2 Access to Data

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC or regulatory authorities may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records to permit trial-related monitoring, audits and inspections.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor. This will not include the subject's contact or identifying information. Rather, individual subject's and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

11.3 Data Recording and Record Keeping

All trial data will be entered on electronic data entry systems that are validated and are maintained in accordance with Standard Operating Procedures.

The subjects will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

12. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol, GCP, and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the conduct of the clinical trial and data generated, are documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 Code of Federal Regulations (CFR) Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 or in compliance with the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or ethical policy statement specific to the country, whichever provides the most protection to human subjects.

13.2 Institutional Review Board/Institutional Ethics Committee

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is screened and enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Subjects

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study. Subjects will be required to sign and date a study consent form prior to any study-related procedures are performed if they meet eligibility requirements of the protocol and wish to participate in the trial. If applicable, it will be provided in a certified translation of the local language.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative [defined as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject’s legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research.

Subjects will be informed that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period. Subjects who decline to participate in this optional research will not provide this separate signature.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB/IEC approved and the participant and/or the legally authorized representative will be asked to read and review the document. The investigator and/or his/her authorized designee will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign and date the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, study documentation, data, and all other study-related information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, auditors, other authorized representatives of the Sponsor including the contract research organization (CRO), if applicable, representatives of the IRB/IEC or the Sponsor supplying study product, the Federal government or its designee and applicable regulatory authorities will be granted direct access to the study participants' original medical records (including but not limited to office, clinic, hospital, or pharmacy records), all documents required to be maintained by the investigator, for verification of clinical trial procedures and/or data, without violating the confidentiality of the participants, to the extent permitted by the law and regulations.

All documents will be stored safely in a secure location to protect confidentiality. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant identification number/code, not by name. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored a Sponsor location. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff at the clinical sites and by authorized representatives of the Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at a Sponsor location.

13.4.1 Research Use of Stored Human Samples, Specimens, or Specimen Data

- Intended Use: Samples and data collected under this protocol may be used to study the effects of the investigational drug on how one's immune system reacts and how the body responds to this type of treatment in treating different types of cancers.
- Storage: Access to stored samples will be limited to specified study personnel/vendor personnel. Samples will be identified by unique subject identification (ID) codes. Samples and data will be stored using subject ID assigned by the Sponsor and investigators.

13.5 Future Use of Stored Specimens

Specimens collected for this study will be analysed and stored at the Sponsor Data Repository or Sponsor-approved vendor.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent related to bio-sample storage, will not be possible after the study is completed.

14. DATA HANDLING AND RECORD KEEPING

14.1 Communication and Data Dissemination Plan

During the study while subjects are receiving treatment with SL-279252, SMC meetings will be held to review relevant data with the investigators or delegates. These meetings will be held once a month (or more frequently if required) during dose escalation to share safety data and communicate results of ongoing analyses. Available safety, PK, pharmacodynamic, and clinical outcome data for all subjects at the time of the scheduled SMC Meeting will be reviewed and summarized. Attendees of SMC meetings will include but not be limited to clinical investigators (or designees), the Sponsor Medical Monitor and Statistician.

The Sponsor will remain in constant contact with the clinical sites during the enrollment period to ensure that cohort enrollment during the dose escalation or dose expansion phases of this study are completed as per protocol. Investigators will be informed about available openings for enrollment on the trial and will be asked to pre-screen subjects to determine their potential for eligibility to avoid over-enrollment. Enrollment will be offered to all sites and slots filled based on the Keyboard Design method.

Dose escalation decisions will be made based on the DLTs observed at the current dose level with guidance provided by the Keyboard design as stated in the study protocol. All dose escalation and dose expansion or safety decisions will be documented in writing with copies maintained at each site and the Trial Master File at the CRO.

14.1.1 Periodic Data Summaries for Investigators and Regulatory Agencies

In addition to standard regulatory reporting requirements for serious AEs and annual reporting, the Sponsor will provide the following data summaries to Investigators and Regulatory Agencies:

- During the conduct of the study, a summary of safety (SAE and AEs) will be provided every 6 months-beginning with the date of the first subject enrolled.

At the end of the dose escalation and dose expansion, an outline of the key findings, including overall safety (SAEs, AEs), tolerability, PK, pharmacodynamic activity and anti-tumor activity; and the justification for the dose and schedule to take forward to Phase 2 (RP2D).

14.2 Data Collection and Management Responsibilities

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be electronically signed by the Principal Investigator or a Sub-investigator listed on the Form FDA 1572. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source documents may include but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and drug accountability records.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record.

Clinical data (including but not limited to AEs, concomitant medications, and expected ARs data) and clinical laboratory data will be entered into the study database, a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered into an electronic data capture system directly from the source documents.

Study data will be entered into eCRFs at the study site. Prior to database lock, programmed computer edit checks and manual checks will be performed to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks are to be resolved as quickly as possible with clarification from study sites.

14.3 Study Records Retention

The Sponsor follows US regulations and ICH guidelines in its retention policy.

US IND regulations (21CFR 312.62c) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug(s) including eCRFs, consent forms, laboratory test results, and medication inventory records be kept on file by the Principal Investigator for 2 years following the date a marketing application is approved for the drug for the indication for which it is being studied. If no application is to be filed or if the application is not

approved for such indication, these records must be kept until 2 years after the investigation has been discontinued and regulatory authorities (i.e., FDA, Health Canada, European Medicines Agency, etc.) have been notified. ICH guidelines indicate that study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to US and ICH policies.

No study records should be destroyed without prior authorization from The Sponsor, the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

14.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations by completing the Sponsor Protocol Deviation Form to the Sponsor Medical Monitor or designee as soon as protocol deviation is identified. A completed copy of the Sponsor Protocol Deviation Form will be maintained in the regulatory file. All deviations must be addressed in study source documents, reported to Sponsor. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site Principal Investigator is responsible for ensuring all study staff understands the local IRB/IEC reporting guidelines and adhere to all related requirements and documentation. Further details about the handling of protocol deviations will be included in the study reference manual.

14.5 Publications and Data Sharing Policy

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

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16. APPENDICES

16.1 ECOG Performance Status Criteria

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.	

16.2 Contraception Requirements

Females or males of reproductive potential must agree to avoid becoming pregnant or avoid impregnating a partner, respectively. Female or males of reproductive potential are required to use adequate methods of birth control from the time of screening (i.e., at least 14 days prior to D1 of SL-279252) through at least 30 days after the last dose of SL-279252.

Definition of Female of Childbearing Potential:
A female subject who is not sterile due to surgery (i.e., from bilateral tubal ligation/occlusion, bilateral oophorectomy, bilateral salpingectomy or complete hysterectomy) or who does not have a congenital or acquired condition that prevents childbearing or who is not naturally post-menopausal for at least 12 consecutive months.

Definition of Female of Non-Reproductive Potential:
Female subjects will be considered of non-reproductive potential if they:

1. Are post-menopausal if defined as amenorrhoeic for 12 consecutive months without an alternative medical cause. In women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 consecutive months of amenorrhea, a single FSH measurement is insufficient;

OR

2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3. Have a congenital or acquired condition that prevents childbearing.

Definition of Male of Non-Reproductive Potential:
Male subjects will be considered of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Highly Effective Methods of Contraception (<1% failure rate):
For contraception, subjects should comply with one of the following:

1. Practice abstinence† from heterosexual activity;

OR

2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - intrauterine device
  - vasectomy of a female subject's male partner
  - contraceptive rod implanted into the skin

- Combination Methods

  - Female Subjects: The following hormonal contraceptives may be used by female subjects and requires use of a male condom for the male partner:
    - oral contraceptive pill (estrogen/progestin pill or progestin-only pill)
    - contraceptive skin patch
    - vaginal contraceptive ring
    - subcutaneous contraceptive injection

  - Male Subjects: The following contraception methods may be used by female partners and requires use of a male condom for the male subject:
    - diaphragm with spermicide
    - cervical cap with spermicide (nulliparous women only)
    - contraceptive sponge (nulliparous women only)
    - hormonal contraceptives including oral contraceptive pill (estrogen/progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs/Independent IECs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the time of screening and at least 14 days prior to D1 of SL-279252 through at least 30 days after the last dose of SL-279252.

16.2.1 Pregnancy Status

In the rare event that β-hCG is elevated as a tumor marker, pregnancy should be excluded. At minimum, this requires obstetrics evaluation, serial β-hCG measurements and ultrasound to exclude pregnancy.

16.3 Keyboard Design

Dose Escalation Rules

Dose escalation for schedule 1 and schedule 2 will follow the keyboard design. The table below in Section 16.3.1 provides the decision rules for the keyboard design when the target DLT rate is 30% (and the acceptable range is 25-33.3%). The columns in the table in Section 16.3.1 represent the number of evaluable subjects at the current dose level, the rows present the action to be taken and the numbers in the table itself are the number of DLTs. As an example, if 3 evaluable subjects have been treated at the current dose level, and 0 of those 3 subjects experience a DLT, then dose escalation can occur, and new subjects will be enrolled 1 dose level higher. If 1 of the 3 subjects experience a DLT, the dose stays the same and new subjects are enrolled at the same dose level. If 2 of the 3 subjects experience a DLT, de-escalation is required, and new subjects are enrolled 1 dose level lower.

See the specific rules for each schedule below for details on how the table in Section 16.3.1 is used. Scenarios have also been provided at the end of this appendix to help illustrate how the keyboard design and table are used in practice.

16.3.1 Keyboard Design Decision Rules

	Number of evaluable subjects treated at the current dose level											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Action												
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.

16.3.1.1 Dose Escalation – Schedule 1

See Section 3.2.4 for the dose levels to be evaluated in schedule 1.

The first subject will be enrolled at Dose Level 1 in a single subject cohort. Single subject cohorts will be enrolled until:

- The subject in a single subject cohort experiences ≥ Grade 2 toxicity (see Section 3.2.5) or a DLT **OR**
- Dose Level 6 is reached without evidence of a DLT or other ≥ Grade 2 toxicity

If a subject in a single subject cohort experiences ≥ Grade 2 toxicity or a DLT, 2 additional subjects will be added at that dose level (for a total of 3). Once a single subject cohort is expanded to 3, having a ≥ Grade 2 toxicity no longer guides dose escalation (only DLTs do) and subsequent cohorts will now include at least 3 subjects. **NOTE:** If a subject in a single subject cohort is not evaluable, an additional single subject cohort should be enrolled at the same dose level. More than 1 subject may be enrolled in a cohort if additional subject(s) are available for dosing after consultation with the Sponsor.

Once cohorts of at least 3 subjects begin enrollment (after expansion of a single subject cohort to 3 or at Dose Level 6), the table in Section 16.3.1 will be used to guide dose escalation.

- There will be a 3-day stagger between the first and second subjects enrolled at a given dose level. **NOTE:** This requirement may change based on emerging data as per the SMC.
- The column corresponding to the total number of evaluable subjects treated at the current dose level should be used to make the appropriate decision (i.e., escalate, stay at the same dose, de-escalate or eliminate).
- If a subject is not evaluable, a decision can still be made based on the total number of subjects who are evaluable at the current dose without enrolling an additional subject (unless all subjects in a cohort are not evaluable*).
- More than 3 subjects may be enrolled in a cohort if additional subject(s) are available for dosing after consultation with the Sponsor.

***NOTE:** If all subjects in a cohort are not evaluable, an additional cohort should be enrolled at the same dose level.

Dose escalation for schedule 1 may continue until:

- The trial is stopped for safety **OR**
- The maximum sample size of 42 subjects is reached **OR**
- The maximum sample size has not been reached but 12 subjects have been enrolled at the current dose level **OR**

- The Sponsor, in consultation with the SMC, decides to stop enrollment in schedule 1 early (e.g., based on safety, pharmacodynamics) and begin enrollment in schedule 2 (see Section 3.2.7)

NOTE: The maximum sample size of 42 may be revised if additional dose levels are evaluated or if more additional subjects (i.e., subjects available for dosing beyond the number required in a cohort) are enrolled than anticipated. The Sponsor, in consultation with the SMC, may also elect to add subjects if additional safety data are needed to select a dose and schedule for the expansion cohorts. Six (6) subjects must be treated at a dose level to confirm safety and tolerability before a dose can be used in an expansion cohort.

16.3.1.2 Dose Escalation – Schedule 2

See Section 3.2.4 for the dose levels to be evaluated if schedule 2 is opened.

Subjects will be enrolled in cohorts of 3, with the table in Section 16.3.1 used to guide dose escalation.

- There will be a 3-day stagger between the first and second subjects enrolled at a given dose level. **NOTE:** This requirement may change based on emerging data as per the SMC.
- The column corresponding to the total number of evaluable subjects treated at the current dose level should be used to make the appropriate decision (i.e., escalate, stay at the same dose, de-escalate or eliminate).
- If a subject is not evaluable, a decision can still be made based on the total number of subjects who are evaluable at the current dose without enrolling an additional subject (unless all subjects in a cohort are not evaluable*).

  More than 3 subjects may be enrolled in a cohort if additional subject(s) are available for dosing after consultation with the Sponsor.

***NOTE:** If all subjects in a cohort are not evaluable, an additional cohort should be enrolled at the same dose level.

Dose escalation for schedule 2 may continue until:

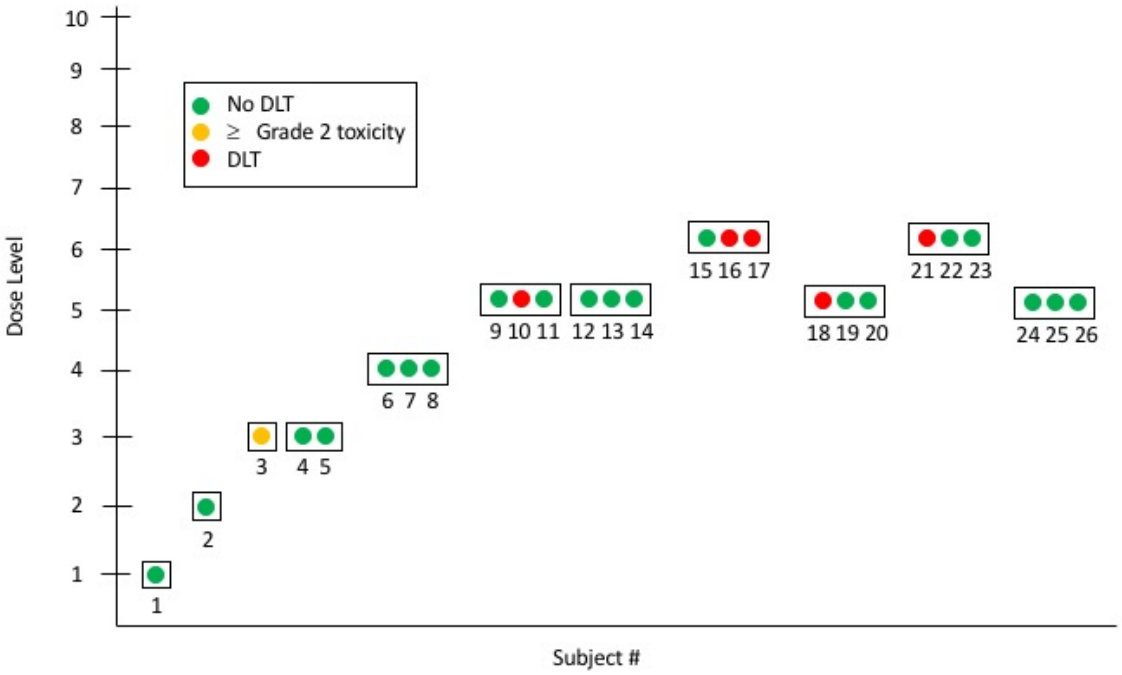
- The trial is stopped for safety **OR**
- The maximum sample size of 15 subjects is reached **OR**
- The maximum sample size has not been reached but 12 subjects have been enrolled at the current dose level **OR**
- The Sponsor, in consultation with the SMC, decides to stop enrollment in schedule 2 early (based on safety.) and resume enrollment in schedule 1 or begin enrollment in dose expansion*

*At least 6 subjects will be enrolled at the dose level to be used during dose expansion and sufficient safety follow-up completed to confirm safety and tolerability (as determined by the SMC) before a decision can be made to begin dose expansion early.

NOTE: The maximum sample size of 15 may be revised if additional dose levels are evaluated or if more additional subjects (i.e., subjects available for dosing beyond the number required in a cohort) are enrolled than anticipated. The Sponsor, in consultation with the SMC, may also elect to add subjects if additional safety data are needed to select a dose and schedule for the expansion cohorts.

16.3.1.3 Keyboard Design Scenarios – Schedule 1

Scenario #1:



NOTE: All subjects in Scenario #1 are evaluable.

1. Subject #1 is enrolled at Dose Level 1 in a single subject cohort. Subject #1 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #2 is enrolled at Dose Level 2 in a single subject cohort.

2. Subject #2 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #3 is enrolled at Dose Level 3 in a single subject cohort.

3. Subject #3 experiences a ≥ Grade 2 toxicity, so 2 additional subjects (Subjects #4 and #5) are enrolled at Dose Level 3. **NOTE:** Having a ≥ Grade 2 toxicity no longer guides dose escalation (only DLTs do) and subsequent cohorts will now include at least 3 subjects.

4. Zero (0) of the 3 total subjects enrolled at Dose Level 3 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #6, #7 and #8) are enrolled at Dose Level 4.

5. Zero (0) of the 3 subjects enrolled at Dose Level 4 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #9, #10 and #11) are enrolled at Dose Level 5.

6. One (1) of the 3 subjects enrolled at Dose Level 5 experience a DLT, so following the table in Section 16.3.1 , the next 3 subjects (Subjects #12, #13 and #14) are also enrolled at Dose Level 5.

7. Only 1 of the 6 total subjects enrolled at Dose Level 5 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #15, #16 and #17) are enrolled at Dose Level 6.

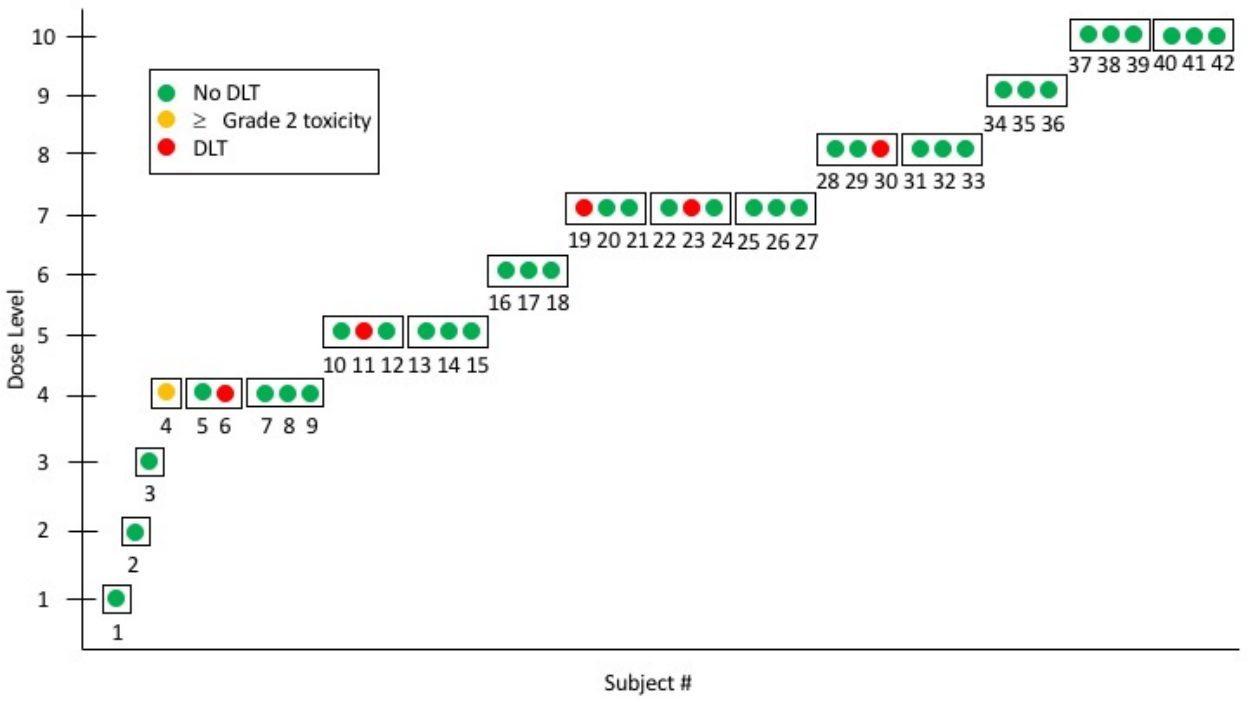
8. Two (2) of the 3 subjects enrolled at Dose Level 6 experience a DLT, so following the table in Section 16.3.1, de-escalation is required and the next 3 subjects (Subjects #18, #19 and #20) are enrolled at Dose Level 5.

9. Two (2) of the 9 total subjects enrolled at Dose Level 5 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #21, #22 and #23) are enrolled at Dose Level 6.

10. Three (3) of the 6 total subjects enrolled at Dose Level 6 experience a DLT, so following the table in Section 16.3.1, de-escalation is required and the next 3 subjects (Subjects #24, #25 and #26) are enrolled at Dose Level 5.

11. The maximum sample size of 42 subjects has not been reached, but 12 subjects have now been enrolled at Dose Level 5, so dose escalation can stop early and the MTD can be determined based on the 26 subjects enrolled.

Scenario #2:



NOTE: All subjects in Scenario #2 are evaluable.

1. Subject #1 is enrolled at Dose Level 1 in a single subject cohort. Subject #1 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #2 is enrolled at Dose Level 2 in a single subject cohort.

2. Subject #2 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #3 is enrolled at Dose Level 3 in a single subject cohort.

3. Subject #3 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #4 is enrolled at Dose Level 4 in a single subject cohort.

4. Subject #4 experiences a ≥ Grade 2 toxicity, so 2 additional subjects (Subjects #5 and #6) are enrolled at Dose Level 4. **NOTE:** Having a ≥ Grade 2 toxicity no longer guides dose escalation (only DLTs do) and subsequent cohorts will now include at least 3 subjects.

5. One (1) of the 3 total subjects enrolled at Dose Level 4 experience a DLT (**NOTE:** the ≥ Grade 2 toxicity is not used for the dose escalation decision), so following the table in Section 16.3.1, the next 3 subjects (Subjects #7, #8 and #9) are also enrolled at Dose Level 4.

6. Only 1 of the 6 total subjects enrolled at Dose Level 4 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #10, #11 and #12) are enrolled in Dose Level 5.

7. One (1) of the 3 subjects enrolled at Dose Level 5 experience a DLT, so following the table in Section 16.3.1, the next 3 subjects (Subjects #13, #14 and #15) are also enrolled at Dose Level 5.

8. Only 1 of the 6 total subjects enrolled at Dose Level 5 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #16, #17 and #18) are enrolled at Dose Level 6.

9. Zero (0) of the 3 subjects enrolled at Dose Level 6 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #19, #20 and #21) are enrolled at Dose Level 7.

10. One (1) of the 3 subjects enrolled at Dose Level 7 experience a DLT, so following the table in Section 16.3.1, the next 3 subjects (Subjects #22, #23 and #24) are also enrolled at Dose Level 7.

11. Two (2) of the 6 total subjects enrolled at Dose Level 7 experience a DLT, so following the table in Section 16.3.1, the next 3 subjects (Subjects #25, #26 and #27) are also enrolled at Dose Level 7.

12. Only 2 of the 9 total subjects enrolled at Dose Level 7 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #28, #29 and #30) are enrolled at Dose Level 8.

13. One (1) of the 3 subjects enrolled at Dose Level 8 experience a DLT, so following the table in Section 16.3.1, the next 3 subjects (Subjects #31, #32 and #33) are also enrolled at Dose Level 8.

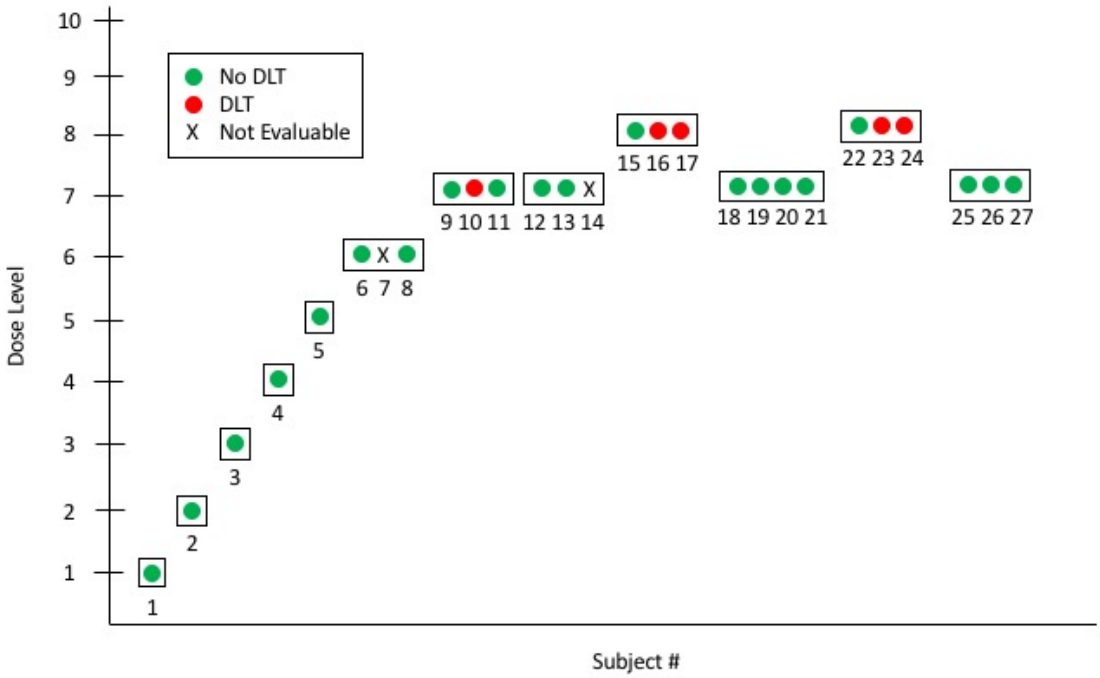
14. Only 1 of the 6 total subjects enrolled at Dose Level 8 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #34, #35 and #36) are enrolled at Dose Level 9.

15. Zero (0) of the 3 subjects enrolled at Dose Level 9 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed and the next 3 subjects (Subjects #37, #38 and #39) are enrolled at Dose Level 10.

16. Zero (0) of the 3 subjects enrolled at Dose Level 10 experience a DLT, so following the table in Section 16.3.1, dose escalation is allowed. However, Dose Level 10 is the highest dose level to be evaluated, so the next 3 subjects (Subjects #40, #41 and #42) are also enrolled at Dose Level 10. This ends dose escalation since the maximum sample size is 48 subjects.

17. The MTD is determined based on the 48 subjects enrolled.

Scenario #3:



1. Subject #1 is enrolled at Dose Level 1 in a single subject cohort. Subject #1 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #2 is enrolled at Dose Level 2 in a single subject cohort.

2. Subject #2 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #3 is enrolled at Dose Level 3 in a single subject cohort.

3. Subject #3 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #4 is enrolled at Dose Level 4 in a single subject cohort.

4. Subject #4 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #5 is enrolled at Dose Level 5 in a single subject cohort.

5. Subject #5 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and the next 3 subjects (Subjects #6, #7 and #8) are enrolled at Dose Level 6. **NOTE:** 3 subjects are enrolled since single subject cohorts are only allowed for the first 5 dose levels (all subsequent cohorts will enroll at least 3 subjects); Having a ≥ Grade 2 toxicity no longer guides dose escalation (only DLTs do).

6. One (1) subject enrolled at Dose Level 6 is not evaluable and 0 of the other 2 subjects enrolled at Dose Level 6 experience a DLT. Following the table in Section 16.3.1 (looking at the column for 2 evaluable subjects treated at the current dose), dose escalation is allowed and the next 3 subjects (Subjects #9, #10 and #11) are enrolled at Dose Level 7.

7. One (1) of the 3 subjects enrolled at Dose Level 7 experience a DLT, so following the table in Section 16.3.1, the next 3 subjects (Subjects #12, #13 and #14) are also enrolled at Dose Level 7.

8. Of the 6 total subjects enrolled at Dose Level 7, 1 subject is not evaluable and only 1 of the other 5 subjects experience a DLT. Following the table in Section 16.3.1 (looking at the column for 5 evaluable subjects treated at the current dose), dose escalation is allowed and the next 3 subjects (Subjects #15, #16 and #17) are enrolled at Dose Level 8.

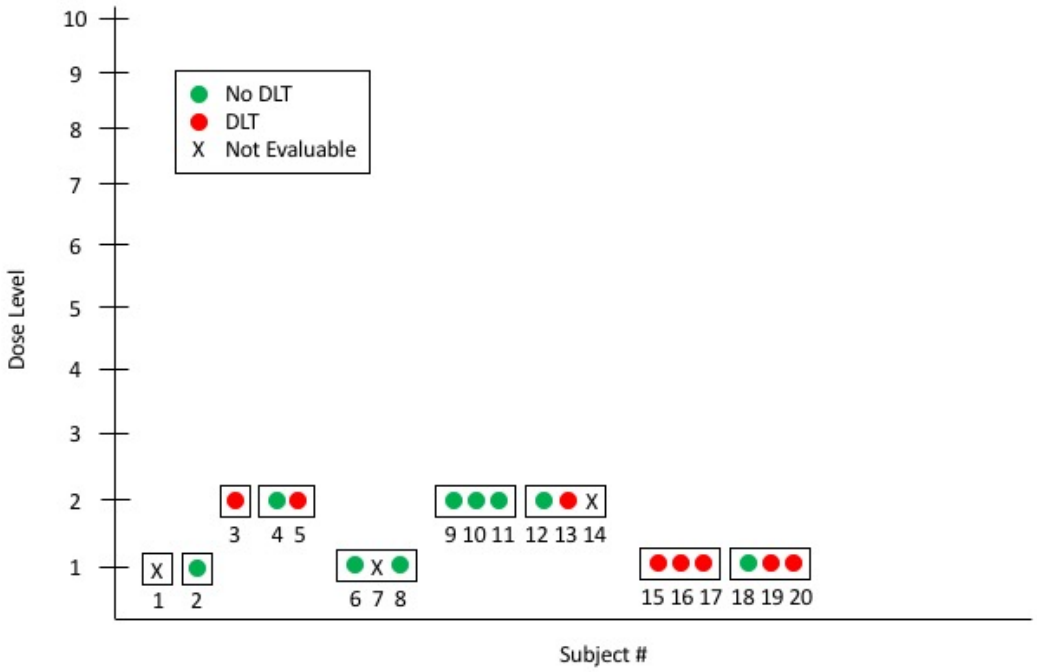
9. Two (2) of the 3 subjects enrolled at Dose Level 8 experience a DLT, so following the table in Section 16.3.1, de-escalation is required and the next 3 subjects (Subjects #18, #19 and #20) are enrolled at Dose Level 7. An additional subject was available for treatment (Subject #21), so was included in the cohort as well (i.e., 4 subjects are enrolled at Dose Level 7).

10. Of the 10 total subjects enrolled in Dose Level 7, 1 subject is not evaluable and only 1 of the other 9 subjects experience a DLT. Following the table in Section 16.3.1 (looking at the column for 9 evaluable subjects treated at the current dose), dose escalation is allowed and the next 3 subjects (Subjects #22, #23 and #24) are enrolled at Dose Level 8.

11. Four (4) of the 6 total subjects enrolled at Dose Level 8 experience a DLT, so following the table in Section 16.3.1, Dose Level 8 is eliminated from the trial. This means that subjects will no longer be enrolled in Dose Level 8, 9 or 10. De-escalation is required and the next 3 subjects (Subjects #25, #26 and #27) are enrolled at Dose Level 7.

12. The maximum sample size of 42 subjects has not been reached, but 12 subjects have now been enrolled at Dose Level 7, so dose escalation can stop early and the MTD can be determined based on the 27 subjects enrolled.

Scenario #4:



1. Subject #1 is enrolled at Dose Level 1 in a single subject cohort. Subject #1 is not evaluable. Because the one subject enrolled at the dose level is not evaluable, another subject (Subject #2), is enrolled at Dose Level 1 in a single subject cohort.

2. Subject #2 does not experience a DLT or a ≥ Grade 2 toxicity, so dose escalation is allowed and Subject #3 is enrolled at Dose Level 2 in a single subject cohort.

3. Subject #3 experiences a DLT, so 2 additional subjects (Subjects #4 and #5) are enrolled at Dose Level 2. **NOTE:** Having a ≥ Grade 2 toxicity no longer guides dose escalation (only DLTs do) and subsequent cohorts will now include at least 3 subjects.

4. Two (2) of the 3 total subjects enrolled at Dose Level 2 experience a DLT, so following the table in Section 16.3.1, de-escalation is required and the next 3 subjects (Subjects #6, #7 and #8) are enrolled at Dose Level 1.

5. Of the 5 total subjects enrolled at Dose Level 1, 2 subjects are not evaluable and 0 of the other 3 subjects experience a DLT. Following the table in Section 16.3.1 (looking at the column for 3 evaluable subjects treated at the current dose), dose escalation is allowed and the next 3 subjects (Subjects #9, #10 and #11) are enrolled at Dose Level 2.

6. Two (2) of the 6 total subjects enrolled at Dose Level 2 experience a DLT, so following the table in Section 16.3.1, the next 3 subjects (Subjects #12, #13 and #14) are also enrolled at Dose Level 2.

7. Of the 9 total subjects enrolled at Dose Level 2, 1 subject is not evaluable and 3 of the other 8 subjects experience a DLT. Following the table in Section 16.3.1 (looking at the column for 8 evaluable subjects treated at the current dose), de-escalation is required and the next 3 subjects (Subjects #15, #16 and #17) are enrolled at Dose Level 1.

8. Of the 8 total subjects enrolled at Dose Level 1, 2 subjects are not evaluable and 3 of the other 6 subjects experience a DLT. Following the table in Section 16.3.1 (looking at the column for 6 evaluable subjects treated at the current dose), de-escalation is required. However, since Dose Level 1 is the lowest dose level, and since the boundary for elimination has not been reached, the next 3 subjects (Subjects #18, #19 and #20) are also enrolled at Dose Level 1.

9. Of the 11 total subjects enrolled in Dose Level 1, 2 subjects are not evaluable and 5 of the other 9 subjects experience a DLT. Following the table in Section 16.3.1 (looking at the column for 9 evaluable subjects treated at the current dose), Dose Level 1 is eliminated from the trial. This means that subjects will no longer be enrolled in Dose Level 1. Since this is the lowest dose level, the trial is stopped for safety and no dose is selected as the MTD.

16.3.1.4 Keyboard Design Scenarios – Schedule 2

If schedule 2 is opened, the table in Section 16.3.1 will be used for all dose escalation decisions and the same principles demonstrated in Scenarios #1-4 apply with the following exceptions:

1. All cohorts will include at least 3 subjects (there are no single subject cohorts).
2. Because there are no single subject cohorts, ≥ Grade 2 toxicities do not guide dose escalation.
3. The maximum total sample size is 15 subjects.

Reference:

Yan F, Mandrekar SJ, and Yuan Y. Keyboard: A Novel Bayesian Toxicity Probability Interval Design for Phase I clinical trials. Clin Cancer Res. 2017;23(15):3994-4003.

16.4 Deauville Criteria

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Reference: Barrington SF, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32(27):3048-3058.

16.5 Cockcroft-Gault Formula for Creatinine Clearance

$$\text{Creatinine clearance (mL/min)}^{1} = \frac{Q \times (140 - \text{age [yr]}) \times \text{ideal body weight [kg]}^{2}}{72 \times \text{serum creatinine [mg/dL]}}$$

Q = 0.85 for females

Q = 1.0 for males

OR

$$\text{Creatinine clearance (mL/min)}^{2} = \frac{K \times (140 - \text{age [yr]}) \times \text{ideal body weight [kg]}^{1}}{\text{serum creatinine [µmol/L]}}$$

K = 1.0 for females

K = 1.23 for males

1. Creatinine clearance has a maximum value of 125 mL/min.
2. Use ideal body weight (IBW) if body weight > 30% of IBW. Otherwise, use bodyweight

Calculation of IBW using the Devine Formula [Devine, 1974]:

Males = 50.0 kg + (2.3 x each inch over 5 ft) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Females = 45.5 kg + (2.3 x each inch over 5 ft) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)

Example:
Male, actual body weight = 90.0 kg; height = 68 inches; IBW = 50 + (2.3) (68 – 60) = 68.4 kg
This subject's actual body weight is >30% over IBW. Therefore, in this case, the subject's IBW of 68.4 kg should be used in calculating the estimated creatinine clearance

Reference:
Devine BJ. Case Number 25 Gentamicin Therapy: Clinical Pharmacy Case Studies. Drug Intell. Clin Pharm. 1974;8:650-655.

16.6 RECIST 1.1 and iRECIST Criteria

16.6.1 RECIST 1.1 Criteria

Measurable disease: Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 millimeter (mm) with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in mm (or decimal fractions of cm). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Malignant lymph nodes: pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis, inflammatory breast disease, lymphangitic involvement of lung or skin, and abdominal masses followed by clinical exam are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions: When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is

added into the sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

16.6.2 Evaluation of Response

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology, specialized imaging or other techniques as appropriate for individual cases) before CR can be accepted. Response should be confirmed in a subsequent scan ≥4 weeks after the scan showing CR.

Partial Response (PR): At least a 30% decrease in the sum of the measures (longest diameters for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-progressive disease. Response should be confirmed in a subsequent scan ≥4 weeks after the scan showing PR.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. Documented at least once ≥4 weeks from baseline.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of progressive disease is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

16.6.3 iRECIST 1.1 Criteria

When using iRECIST, the definitions of measurable and non-measurable lesions still follow RECIST 1.1. The principles used to establish an objective tumor response when using iRECIST are largely unchanged from RECIST 1.1, however, responses assigned using iRECIST have a prefix of "i" (e.g., "immune" complete response [iCR]) to differentiate them from responses assigned using RECIST 1.1.

The major change is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage. This adaptation accounts for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression. Therefore, iRECIST requires confirmation of progression.

Confirming Progression: iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks after iUPD. iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following criteria:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions

- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

- If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline).

New Lesions: New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions) and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the eCRF.

Progressive disease is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

iRECIST Time Point Response Table

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response (TPR)	
			No prior iUPD	Prior iUPD
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NL were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: previously identified T lesion iUPD SOM ≥5 mm and/or NT lesion iUPD (prior assessment need not be unequivocal PD)

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response (TPR)	
			No prior iUPD	Prior iUPD
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/ • previously identified NT lesion iUPD (prior assessment need not be unequivocal PD) • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on: • increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no pseudo-progression of disease (PSPD) occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.
PD = progressive disease; SOM = sum of measurements
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

16.7 RECIL

Target Lesions: Target lesions should be selected from those with the largest size that can be reproducibly measured and should preferably represent multiple sites or organs. In most cases, lymph nodes can be considered target lesions if the lymph node's longest diameter is ≥ 15 mm. Extra-nodal lesions are selected as target lesions if they have a soft tissue component, based on their size, and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of ≥ 15 mm.

Non-target Lesions: All other lesions including measurable lesions over and above the 3 target lesions should be identified as non-target lesions and should be recorded at baseline without the need to measure them. In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available. Non-target lesions should be reported as present, absent, or unequivocal progression.

Bone marrow: A bone marrow biopsy would be performed as a part of staging. In participants with positive FDG-PET uptake may obviate the need for a bone marrow biopsy. Participants with HL without FDG update in the bone marrow or presence of B-symptoms do not need a bone marrow biopsy at baseline, as bone marrow biopsy in this situation is extremely unlikely to modify stage.

16.7.1 Evaluation of Response

Complete Response: Complete disappearance of all target lesions by CT scan with complete normalization of FDG-PET (Deauville score 1–3 [see Appendix Section 16.4]) uptake in all areas and bone marrow biopsy negativity (if it was positive or unknown at baseline). If pretreatment PET scan was negative, all lymph nodes that measure ≥ 15 mm in the long axis should regress to < 10 mm. CR is also defined as achievement of a PR by CT scan (> 30% decrease in sum of longest diameters of target lesions) plus normalization of FDG-PET in FDG-avid lymphoma. Because many novel agents may alter glucose uptake and/or metabolism, normalizing FDG-PET imaging alone is not sufficient by itself to determine CR status unless accompanied with a significant decrease (>30%) decrease in the sum of diameters. Accordingly, a reduction in the sum of diameters by ≤30% with normalization of FDG-PET uptake should not be considered a CR unless documented by a negative tissue biopsy.

In cases where pretreatment baseline tumor burden is low, with only a few lesions measuring around 2 cm in longest diameter, treatment effect may shrink the long axis of a target lymph node to normal values of <10 mm. However, even though the lymph node is now within normal size range, consistent with CR, the percentage of diameter reduction may be <30% (less than PR). In these cases, a normalized diameter of "0 or resolved" should be used to calculate the sum of diameter, and therefore ensuring accurate response designation.

Partial Response: A ≥ 30% decrease in the sum of longest diameters of target lesions but not a CR, positive FDG-PET (Deauville score 4–5), any bone marrow involvement, no new lesions. If one or more target lesions grew but the sum of the diameters remains ≤30% of the baseline measurement, and no new lesions appear, the response should be designated a PR.

Minor Response: ≥ 10% decrease in the sum of longest diameters of target lesions but not a partial response, any FDG-PET findings, any bone marrow involvement, no new lesions.

Stable Disease: < 10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions, any FDG-PET findings, any bone marrow involvement, no new lesions.

Progressive Disease: > 20% increase in the sum of longest diameter of target lesions; for small lymph nodes of < 15 mm posttherapy, minimum absolute increase of 5 mm and long diameter > 15 mm; appearance of new lesion; any FDG-PET finding; any bone marrow involvement; new or no new lesions.

Progressive Disease After Initial Response: after initial response, and in the absence of appearance of new lesions, progressive disease is defined as an increase of the nadir sum of diameters by > 20%.

Response Assessment in Participants Receiving Immune-Modulating Agents, Including Checkpoint Inhibitors: to account for potential 'pseudoprogression,' immune-related response criteria should be used, requiring confirmation of progressive disease on two consecutive scans at least 4 weeks apart and inclusion of new lesion measurements in the total tumor burden.

Appearance of New Extranodal Lesion: A minimum of 1 cm in largest diameter of new extranodal lesions is required to confirm progressive disease. New smaller but suspicious lesions should be designated as equivocal; if later confirmed (by CT or biopsy) as due to lymphoma, the documented date of disease progression should be the date of identification as equivocal.

Disseminated Disease: The status of nontarget lesions should be accounted for before formulating the final response status. The International Working Group statement provides a recommended approach to response designation involving the best response of target and nontarget lesions.

16.7.2 Response Designations in Lymphoma Table

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD (PR, MR, SD)	No	PR
CR	Unevaluable	No	UE
CR	No	No	CR
PR	Unevaluable	No	UE
PR	CR, Non-CR/Non-PD	No	PR

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
PR	No	No	PR
MR	Unevaluable	No	UE
MR	CR, Non-CR/Non-PD	No	MR
MR	No	No	MR
SD	Unevaluable	No	UE
SD	CR, Non-CR/Non-PD	No	SD
SD	No	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

PD = progressive disease

16.8 Blood Requirements for Study

Total Blood Requirements

Schedule	Screening (mL)	Cycle 1 (mL)	First 30 Days (mL)	Cycle 2 (mL)	Cycle 3/4 (mL)	Cycles ≥5 (mL)
Dose Escalation Schedule 1	17	147	201	82	22	18
Dose Escalation Schedule 2	17	147	201	95	32	28
Dose Expansion Cohort Schedule 1	17	142	196	71	22	18
Dose Expansion Cohort Schedule 2	17	142	196	81	32	18

Dose Escalation Schedule 1 – Blood Requirements

Test Sample	Sample volume (mL)	Screening (mL)	Cycle 1 (mL)	First 30 Days (mL)	Cycle 2 (mL)	Cycle 3/4 (mL)	Cycles ≥ 5 (mL)
Hematology profile	2	2	12	16	8	4	4
Chemistry profile	3	3	18	24	12	6	6
C Reactive Protein & Ferritin	2	2					
Coagulation profile	3	3	18	24	12		
Thyroid test	2	2		2	2	2	2
Antiviral testing (HBV/HCV)	5	5					
PK, ADA, Cytokines	2-7		55	73	18	10	6
Complement	2		12	18	6		
Immunophenotyping/ Receptor occupancy	4		32	44	24		
TOTAL		17	147	201	82	22	18

Dose Escalation Schedule 2 – Blood Requirements

Test Sample	Sample volume (mL)	Screening (mL)	Cycle 1 (mL)	First 30 Days (mL)	Cycle 2 (mL)	Cycle 3/4 (mL)	Cycles ≥ 5 (mL)
Hematology profile	2	2	12	16	12	8	8
Chemistry profile	3	3	18	24	18	12	12
C Reactive Protein & Ferritin	2	2					
Coagulation profile	3	3	18	24	15		
Thyroid test	2	2		2	2	2	2
Antiviral testing (HBV/HCV)	5	5					
PK, ADA, Cytokines	2-7		55	73	18	10	6
Complement	2		12	18	6		
Immunophenotyping/ Receptor occupancy	4		32	44	24		
TOTAL		17	147	201	95	32	28

Dose Expansion Cohort Schedule 1 – Blood Requirements

Test Sample	Sample volume (mL)	Screening (mL)	Cycle 1 (mL)	First 30 Days (mL)	Cycle 2 (mL)	Cycle 3/4 (mL)	Cycles ≥5 (mL)
Hematology profile	2	2	12	16	6	4	4
Chemistry profile	3	3	18	24	9	6	6
C Reactive Protein & Ferritin	2	2					
Coagulation profile	3	3	12	18	6		
Thyroid test	2	2		2	2	2	2
Antiviral testing (HBV/HCV)	5	5					
cfNA	10		20	20			
PK, ADA, Cytokines	2-7		36	54	18	10	6
Complement	2		12	18	6		
Immunophenotyping/ Receptor occupancy	4		32	44	24		
TOTAL		17	142	196	71	22	18

Dose Expansion Cohort Schedule 2 – Blood Requirements

Test Sample	Sample volume (mL)	Screening (mL)	Cycle 1 (mL)	First 30 Days (mL)	Cycle 2 (mL)	Cycle 3/4 (mL)	Cycles ≥5 (mL)
Hematology profile	2	2	12	16	10	8	4
Chemistry profile	3	3	18	24	15	12	6
C Reactive Protein & Ferritin	2	2					
Coagulation profile	3	3	12	18	6		
Thyroid test	2	2		2	2	2	2
Antiviral testing (HBV/HCV)	5	5					
cfNA	10		20	20			
PK, ADA, Cytokines	2-7		36	54	18	10	6
Complement	2		12	18	6		
Immunophenotyping/ Receptor occupancy	4		32	44	24		
TOTAL		17	142	196	81	32	18

AD HOC Labs

Test Sample	Sample volume (mL)
CBC (mL)	3
C reactive protein (mL)	1
PK & ADA (mL)	6
Cytokines & chemokines (mL)	1
Immunophenotyping (mL)	4
TOTAL	15

16.9 Summary of Protocol Changes – Amendment 01

Editorial Changes:

Title page
Approval date changed to December 11, 2018 and version number changed to 01
Table of Contents
Updated to include new Appendix Section 16.9 and page numbers revised
List of Tables and List of Figures
Updated page numbers
Synopsis
Statistics Section: changed CRS to IRR since sequential boundaries in dose expansion will be used to specifically monitor IRRs (including CRS) and toxicities leading to discontinuation of SL-279252.
Literature and intext references to IB updated
Appendix 16.9
New appendix added summarizing protocol changes for Amendment #1

Clinical Issue #1 – Upper Bound of Target DLT rate lowered to 33%:

Protocol Synopsis
Statistics Section: revised language to reflect upper bound of target DLT rate lowered and is of 25-33.3%
Section 9.1
Text modified to indicate reflect target DLT range as 25-33.3% range.
Section 9.2.1
Revised text added to reflect target DLT range as 25-33.3%.
Section 9.4.1.1
The MAD will be reported, or the MTD will be estimated using isotonic regression (based on the DLTs observed in evaluable subjects). A MAD will be reported if a schedule is fully evaluated, but the DLT rate never reaches the target range of 25-33.3%.
Appendix Sections 16.3 and 16.3.1
Revised dose escalation rules for Keyboard Design decision rules in to reflect target DLT range of 25 to 33.3%

Issue #2 – Dose expansion cohorts will enroll subjects at dose levels determined as safe per the Keyboard Design

Section 3.1.2
Study Schema's supporting text revised to clarify that only dose levels cleared for safety per the Keyboard Design with a minimum of 6 subjects treated at that dose level will be expanded
Section 3.3.1
Clarifying text added that only dose levels that have been cleared for safety per the Keyboard design with a minimum of 6 subjects treated at that dose level will be expanded

Issue #3 – Grade 3 or greater CRS is a DLT

Protocol Synopsis

Definition of DLTs section: removed Grade 3 CRS that resolves to less than or equal to Grade 1 within 24 hours with appropriate management as an exception to DLT definition

Section 3.2.6

Removed Grade 3 CRS that resolves to less than or equal to Grade 1 within 24 hours with appropriate management as an exception to DLT definition

Issue #4 – Modified guidelines on management of all grades of CRS and IRRs

Section 3.5.1

Accompanying text associated with table changed to state that in the event of any Grade IRR (including CRS), subjects will be admitted for closer observation until resolution of symptoms

Infusion or hypersensitivity reactions management guideline changed

- Management guidelines for IRRs (all grades) changed to state that in the event of any Grade IRR subjects will be admitted for closer observation until resolution of symptoms
- Grade 3 IRR: removed text allowing subject to be monitored for resolution of symptoms without admission for closer observation

CRS management changes

- Management guidelines for CRS (all grades) changed text to state that in the event of any Grade CRS subjects will be admitted to the hospital for closer observation until resolution of symptoms and removed all contradictory statements to this requirement
- **Grade 2 CRS:**
  - removed text allowing subject to be monitored for resolution of symptoms without admission for closer observation
  - Added text to interrupt IP and not restart IP until symptoms are returned to less than or equal to 1 for at least 3 days. Once symptoms have resolved can administer IP per next scheduled time point
  - Added text to clarify that following Grade 2 CRS the next two subsequent infusions of SL-279252 must be administered in an inpatient setting for prolonged observation (e.g., 24 hours)
  - Added text stating that for subsequent infusions, following a Grade 2 CRS event, may consider pre-medication with dexamethasone 20 mg and other agents per institutional guidelines
- **Grade 3 CRS:**
  - Added text to Interrupt IP and not-restart IP until symptoms are returned to grade less than or equal to 1 for at least 3 days. Once symptoms have resolved, administer dose per next scheduled time point
  - Added text that for Grade 3 CRS, may consider re-challenge at the next lower dose level after consultation with medical monitor. After a Grade 3 CRS event, subjects must be pre-medicated with high dose steroids prior to the infusion of SL-279252. If there is no evidence of CRS at the reduced dose level, premedication with high dose steroids may be omitted for subsequent infusions. The two subsequent infusions of SL-279252 after an event of Grade 3 CRS should be administered in an inpatient setting for prolonged observation (e.g., 24 hours).

- Added text that any subject that experiences recurrence of Grade 3 CRS following re-treatment must be permanently discontinued from study treatment.
- Added text that any subject that experiences recurrence of Grade 3 CRS following re-treatment must be permanently discontinued from the study treatment.

Section 5.6

Text revised to indicate that in the event of any Grade IRR (including CRS), subjects will be admitted for closer observation until resolution of symptoms.

Issue #5 -Modified dose escalation between second and third dose levels to half-log increment

Protocol Synopsis

- Planned sample size section: changed sample size to approximately 42 to 87 subjects
- Dose escalation scheme section: in table changed dose level 3 to 0.003 mg/kg, In addition, footnote c of table notes that half-log incremental increases will not be exceeded after dose level 2, and option to explore 10 dose levels or more during the study on Schedule 1 or additional dose levels on schedule 2 as possibility if safety allows.

Section 3.1.1

Revised wording to reflect changes in sample size estimates to evaluate up to 10 or more dose levels. The maximum planned sample size for dose escalation is 42 subjects if only Schedule 1 is evaluated and, if Schedules 1 and 2 are evaluated in dose escalation, the maximum planned sample size is 57. Overall, the total sample size estimate for this study is 72 subjects assuming only Schedule 1 is evaluated in dose escalation and 87 subjects if Schedules 1 and 2 are fully evaluated.

Section 3.1.2

Study schema revised to reflect addition of dose level 3 (0.003 mg/kg) to dose escalation levels

Section 3.2.4

- Text changed to clarify that first two dose levels will be increased in log increments and beyond dose level 2, dose escalations will not exceed half-log increments
- Table 5 revised to reflect 10 dose levels and insertion of dose level 3 = 0.003 mg/kg and footnote c of table revised to note that escalation with not exceed half-log increments
- Text describing evaluation of schedule 2 indicates that 0.1 mg/kg is dose level 6 then starting dose on schedule 2 will be 0.03 mg/kg (dose level 5) or lower

Section 4.5

Text modified to reflect revisions to sample size accrual goal (i.e., 72-87 subjects) to accommodate addition of dose level 3.

Section 9.1

Text modified to indicate 10 dose levels planned and 42 subjects enrolled during dose escalation if Schedule 1 is fully evaluated.

Section 9.2.1

Maximum estimated sample size for schedule 1 changed to 42 for schedule 1.

Section 9.2.1.1

The first and second set of simulations for Schedule 1 revised to reflect 10 dose levels and maximum sample size of 42 subjects for dose escalation

Section 9.2.1.2

If both Schedule 1 and 2 are evaluated, the planned maximum total sample size during dose escalation is 57 subjects. If only Schedule 1 is evaluated (which is expected), the planned maximum total sample size during dose escalation is 42 subjects.

Appendix Sections 16.3.1.1 (Dose Escalation on Schedule 1)

Maximum sample size is 42 subjects

Issue #6 – Modified dose escalation scheme such that dose level 9 corresponds to a dose of 3.0 mg/kg of SL-279252 and dose level 10 corresponds to a dose of 6.0 mg/kg of SL-279252.

Protocol synopsis dose escalation scheme

- Dose level 9 modified to 3.0 mg/kg SL-279252
- Dose level 10 modified to 6.0 mg/kg SL-279252

Table 5 in Section 3.2.4

- Dose level 9 modified to 3.0 mg/kg SL-279252
- Dose level 10 modified to 6.0 mg/kg SL-279252

Issue #1 (i.e., upper bound of target DLT range = 33.3%) **and Issue #5** (i.e., addition of dose level 3 = 0.03 mg/kg)

Appendix Section 16.3.1.3.

Keyboard Design Scenarios 1-3 for dose escalation on Schedule 1 were revised to reflect changes in upper bound of DLT target range to 33.3% with 42 subjects as maximum sample size. The 4th scenario stops the study with no dose selected as the MTD.

Issue #7– Modified follow up for ADA until resolution to baseline if subject has positive ADA test on study or within 7-30 days of last dose of SL-279252

Footnote L in SOA Tables in Sections 6.1, 6.2, 6.3 and 6.4

New text added: If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline. If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

Dose Escalation PK Supplementary Table 8 in Section 6.1.1 and Dose Escalation PK Supplementary Table 12 in Section 6.2.1

- New footnote # 4 added : If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline.
- New text added to Tables 8 and 12: If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

Dose Expansion PK Supplementary Table 15 in Section 6.3.1 and Dose Expansion PK Supplementary Table 18 in Section 6.4.1

- New footnote # 5 added : If subject has positive ADA test on D1 of cycle 13, then follow up predose samples for PK/ADA should be collected every ~90 days on D1 of subsequent treatment cycles until ADA resolves to baseline.
- New text added to Tables 15 and 18: If ADA positivity is detected within 7-30 days after the last dose of SL-279252, then follow up testing for PK/ADA should be performed at monthly intervals until ADA resolves to baseline.

16.10 Summary of Protocol Changes – Amendment 02

(Country-specific Amendment for Belgium)

Editorial Changes:

Document Headers
Updated to denote version 02 of protocol
Title page
Approval date changed to 06 June, 2019 and protocol version number changed to version 02
Summary of Amendment Changes for Amendment 2
Added new summary of changes for Amendment 2 after the Title Page and summary of changes for Amendment 1
Table of Contents
Updated to include new section on drugs to be used with caution and new Appendix Section 16.10
Page numbers revised
Abbreviations List
Added CYP450 to abbreviations list
Literature References
Added new reference (Evers et al., Drug Metabolism and Disposition 2013;41:1598-1609)

Clinical Issue #1 – Double-barrier methods for contraception in female subjects are inadequate as they do not have a < 1% failure rate.

- Clarified in section 16.2 acceptable forms of contraception for male and female subjects of childbearing potential in the study.

Issue #2 – Medications to be used with caution with SL-279252 which is a therapeutic protein that induces the release of cytokines including IL-6. Cytokine release may impact CYP450 enzyme activity.

- Added new section (3.4.3 Medications to be used with Caution) and new text to the protocol noting that drugs that are substrates of CYP450 enzymes should be used with caution when coadministered with SL-279252.

16.11 Summary of Protocol Changes – Amendment 03

This Global amendment encompasses changes made to the protocol described in Appendix 16.10 (Country-specific Amendent 02 for Belgium) plus the additional changes outlined below.

Minor Editorial Changes:

Document Headers
Updated to denote version 03 of protocol
Title page
Approval date changed to 11 October, 2019 and protocol version number changed to version 03
Summary of Amendment Changes for Amendment 2
Added new summary of changes for Amendment 03 after the Title Page
Table of Contents
Updated to include new section on drugs to be used with caution and new Appendix Section 16.10 (for countries outsided of Belgium) and new Appendix section 16.11.
Page numbers revised
Abbreviations list
TTR – time to tumor response added

Issue #1: Amendment 02 changes included for countries outside of Belgium

- see Appendix 16.10

Issue #2 and Issue #3e: Pharmacodynamic cohorts are now included for enrollment during dose escalation

- Synopsis and Section 4.5:
  - Planned sample size increases by approximately 6 subjects in total to 78 and 93 subjects from 72 and 87.
- Study Schema
  - New text added to caption under schema: A pharmacodynamic cohorts may also be explored during dose escalation as described in Section 3.1.
- Section 3.1:
  - New text added: **Pharmacodynamic Cohorts in Dose Escalation**: 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. As a result, the maximum planned sample size estimate in dose escalation may increase by approximately 6 subjects and the overall total planned sample size estimates would increase accordingly. Subjects in the pharmacodynamic cohorts will be followed per the Dose Escalation Schedule of Assessment (SOA) tables provided in Sections 6.1 (schedule 1) and 6.2 (schedule 2).
- Section 9.1:

  - New text added: During the dose escalation, additional subjects (approximately 6) may be enrolled into a pharmacodynamic cohort to obtain additional pharmacodynamic data at select dose levels that have previously completed evaluation for safety and not exceeded the MTD.
- Section 9.2.1:
  - New text added: The planned sample size for the dose escalation part of the study is 63 subjects. The planned number of subjects to obtain additional pharmacodynamic data at select dose levels is approximately 6 subjects.
  - Minor edits to text included

Issue #3: Editorial changes to remove unclear text and to further clarify intent of study plans are provided throughout the document to study objectives, statistical plans, definitions of study populations, etc).

a) Time to tumor response added as an endpoint for assessment of antitumor activity,
b) Minor response removed for subjects with lymphoma as part of the clinical benefit rate definition;
c) iSD as part of clinical benefit rate defined as ≥ 16 weeks duration instead of 12 weeks
d) Refined definitions of populations under study in statistical section
e) Revised sample size estimates to accommodate the addition of pharmacodynamic cohorts for enrollment during dose escalation
f) Clarification of MTD selection based on isotonic estimate

- Objectives and outcome measures outlined in Synopsis and Section 2.0 **(Issues 3a-c)**
  - TTR added as an outcome measure for antitumor activity
  - CBR definition for iSD is ≥16 weeks
  - Minor response is removed from CBR
- Section 5.4
  - Removed sentence stating all doses should be rounded up to the nearest mg per institutional standard
- Footnote b to SOA Tables 6.1, 6.2, 6.3 and 6.4
  - Text modified to clarify window for screening and cycle 1, day 1 assessments ie, A physical exam, weight and ECOG performance status obtained for a subject within 24 hours prior to dosing on Cycle 1, Day 1 is acceptable.With the exception of Screening and Day 1 visitsasessments and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window.
- Section 6.9.2.2
  - New Text added: Archival tissue may be accepted as a pre-treatment specimen in lieu of a fresh biopsy if the subject has not undergone treatment since time of specimen collection and if the sample was collected via core needle biopsy.
- Section 8.1.1
  - Removed text related to iRECIST best overall response
  - Removed Table 21: iRECIST Best Overall Response and removed reference to Table 21 in Appendix Section 16.6.3
- Section 9.2.1.2
  - Minor edit to text referring to dose escalation process
- Section 9.3 Table defining analysis populations revised for clarity to alignment with Statistical Analysis Plan (SAP) **(Issue 3d)**

  - Enrolled subjects are all subjects who sign the main study ICF
  - All Treated Population notes that Safety data will be evaluat based on this population
  - Removed definition of safety population from table since it is defined as part of all treated population
  - DLT Evaluable (removed text limiting to dose escalation) and added new text: All subjects in the All Treated population who receive at least 2 doses of SL-279252, 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.
  - Removed text from DLT Evaluable: ~~A subject who has sufficient safety data available to conclude that a DLT did or did not occur (see Section 3.2.6)~~
  - Efficacy Evaluable Population revised text as follows: A subject who received at least one post-baseline disease ~~first~~ assessment ~~at the 8 week time point~~ or had progressed or died before the first post-baseline disease assessment. Removed text as follows: ~~This is the primary population for efficacy analyses.~~
  - Pharmacodynamic Population added new text: The pharmacodynamic population will be used for the pharmacodynamic data analysis.
- Section 9.4
  - Clarified that the planned statistical analyses for pharmacokinetic and specific pharmacodynamic markers that will be utilized in dose selection will also be summarized.
- Section 9.4.1.1 **(Issue 3F)**
  - Modified text as follows: Changes in safety assessments (e.g., laboratory parameters, ~~vital signs~~, etc.) will also be summarized using descriptive statistics ~~(e.g., mean, standard deviation, median, minimum and maximum values)~~.
  - Added new text: Specifically, the MTD is selected as the dose for which the isotonic estimate of the DLT rate is closest to the target DLT rate of 0.3. If there are ties, we select the highest dose level when the isotonic estimate is lower than the target DLT rate; and we select the lowest dose level when the isotonic estimate is greater than the target DLT rate.
- Section 9.4.1.2
  - Modified text to clarify that summaries will be presented for each dose expansion cohort separately.
  - Modified text to clarify that the All Treated population will be used for analyses.
- Section 9.4.2
  - Removed sentence stating the primary analysis will be subjects evaluable for efficacy.
- Section 9.4.3
  - Modified text to state the following: If appropriate, TTR, DOR, progression-free survival and overall survival may also be summarized using the Kaplan-Meier method, with medians reported along with 95% confidence intervals.

Issue #4: Receptor occupancy samples will also be collected in dose expansion cohorts (no longer limited to collection in dose escalation cohorts).

- Synopsis under exploratory objectives section and Section 2.0 under exploratory objectives now includes the following outcome measure for dose expansion
  - 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
- Section 6.6.6 under Flow cytometry panel receptor occupancy panel: Removed text that restricts collection of this panel in dose escalation cohorts only

- Section 6.9.1.2 and Section 9.4.3 include statement that receptor occupancy will be measured during dose escalation and dose expansion
- SOA tables for dose expansion (Sections 6.3 for Schedule 1 and 6.4 for Schedule 2) and dose expansion-related supplementary tables 16 and 19 in sections 6.3.2 and 6.4.2, respectively now include collection of receptor occupancy samples
- Footnote m for SOA tables in 6.3 and 6.3 now notes that receptor occupancy samples are being collected

Issue #5: Additional time points for collection of biomarker samples (immunophenotyping and receptor occupancy) in cycle 2 on days 15 and 16 have been added that impact schedule of assessment and supplementary tables for dose escalation and dose expansion cohorts.

- SOA Tables for dose escalation (Sections 6.1 for Schedule 1 and 6.2 for Schedule 2) and dose expansion (Sections 6.3 for Schedule 1 and 6.4 for Schedule 2) now include collection of immunophenotyping and receptor occupancy samples during cycle 2 on days 15 and 16
- Supplementary table 9 in section 6.1.2 and supplementary table 13 in section 6.2.2 have been updated to show collection of predose samples for all biomarkers, 2 h post dose sample for receptor occupancy and 24 h post dose samples for assessment of receptor occupancy and immunophenotypind during cycle 2 on days 15 and 16. Complement samples will NOT be collected during cycle 2 on days 15 and 16.
- Supplementary tables 6.3.2 and 6.4.2 have been updated to show collection of predose samples for all biomarkers, 2 h post dose sample for receptor occupancy and 24 h post dose samples for assessment of receptor occupancy and immunophenotyping during cycle 2 on days 15 and 16. Complement samples will NOT be collected during cycle 2 on days 15 and 16.
- New text added as Footnote r in SOA table 6.3 states: **Cycle 2 Days 15 and 16**: Collect biomarker samples outlined in Table 16 in Section 6.3.2. Refer to the SLM for details.

Issue #4 and #5 described above:

- Modified Appendix 16.8 to reflect changes in blood volumes collected because of additional biomarker samples being collected in dose escalation and dose expansion cohorts

16.12 Summary of Protocol Changes – Amendment 04

The primary purpose for this Global amendment is to revise eligibility criteria and tumor types included for study participation. The planned tumor types needed to complete enrollment in expansion cohorts necessitates the addition of clinical sites. In addition, minor editorial and formatting changes were made.

Minor Editorial Changes:

Document Headers
Updated to denote version 04 of protocol
Title page
Approval date changed to 24 February, 2020 and protocol version number changed to version 04
Table of Contents
Updated to include new section on drugs to be used with caution and new Appendix Section 16.12
Page numbers revised
Abbreviations list
DLBCL – removed
Synopsis
Revised eligibility criteria to align with text changes made in the main body of the protocol as described below.

Issue #1 – Subjects with DLBCL are no longer eligible for study participation.

- Section 1.3 revised text
  - This first-in-human Phase 1 study will evaluate the safety, tolerability, PK, anti-tumor and pharmacodynamic effects of SL-279252 to identify the dose and schedule i.e., recommended Phase 2 dose (RP2D) for future development. The trial will enroll patients with tumor types that have demonstrated benefit from anti-PD1/L1 inhibitor therapy i.e., melanoma, non-small cell lung cancer (NSCLC), urothelial cancer, head and neck squamous cell carcinoma (HNSCC), squamous cell cervical cancer, gastric or gastro-esophageal junction (GEJ) adenocarcinoma, squamous cell carcinoma of the anal canal (SCCA), squamous cell carcinoma of the skin (Skin-SCC), renal cell cancer (RCC), Hodgkin's lymphoma (HL), ~~diffuse large B cell lymphoma (DLBCL)~~ and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding central nervous system (CNS) malignancies.
- Section 3.1 revised text
  - 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, ~~DLBCL,~~ MSI-H or MMRD solid tumors excluding CNS malignancies. The tumor types for dose expansion (up to 4 histologies) will be determined after review of data collected during dose escalation, and will be selected from the dose escalation list of malignancies.
- Section 3.1.2 Study schema
  - Removed DLBCL as tumor type included in schema
- Section 4.2 Inclusion Criterion #2
  - Removed DLBCL as tumor type for inclusion in the study

- Appendix 16.7 revised text
    - **Bone marrow**: ~~Participants with DLBCL with a negative FDG PET uptake in the bone marrow, does not rule out bone marrow involvement, especially discordant histology.~~ A bone marrow biopsy would be performed as a part of staging. In participants with positive FDG-PET uptake may obviate the need for a bone marrow biopsy. Participants with HL without FDG update in the bone marrow or presence of B-symptoms do not need a bone marrow biopsy at baseline, as bone marrow biopsy in this situation is extremely unlikely to modify stage.

Issue #2 – Revised Eligibility criteria

- Text deleted and new text added to Inclusion criterion #2 in Section 4.2
    - Subject has a histologically confirmed diagnosis of one of the following unresectable locally advanced or metastatic malignancies: melanoma, non-small cell lung cancer (squamous, adeno, or adeno-squamous), urothelial cancer, squamous cell carcinoma of the head and neck, squamous cell cervical cancer, gastric or gastro-esophageal junction adenocarcinoma, squamous cell carcinoma of the anal canal, squamous cell carcinoma of the skin, renal cell cancer, Hodgkin's lymphoma, ~~diffuse large B-cell lymphoma~~, and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding CNS malignancies. MSI and MMRD testing results as per institution is acceptable. NOTE: The tumor types for dose expansion (up to 4 histologies) will be determined after review of data collected during dose escalation, and will be selected from this list of malignancies.

      New Text:
        - Head and neck cancers: Subjects must have primary tumor locations in the oropharynx, oral cavity, hypopharynx, or larynx. Primary tumor sites of nasopharynx, maxillary sinus, paranasal, and unknown primary are excluded.
        - Melanoma: Subjects with a diagnosis of uveal or ocular melanoma are excluded.
        - Non-small cell lung cancers: Subjects with a known EGFR sensitizing (activating) mutation or an ALK fusion are excluded.
- New text added to Inclusion criterion #11 in Section 4.2
    - All AEs resulting from prior anti-cancer immunotherapy have resolved (NOTE: exceptions include alopecia, vitiligo, and endocrinopathies adequately treated with hormone replacement).

      New Text:
        - Subjects that were discontinued from prior PD-1/L1 therapy due to immune-related adverse events are not eligible
- New text added to Exclusion criterion #1 in Section 4.3
    - Has received more than two prior checkpoint inhibitor containing treatment regimens (regimen refers to either monotherapy or combination immunotherapies) or has had prior treatment with an OX40 agonist.
        - Prior PD-1/L1 therapy is not required.
- Text deleted and new text added to Exclusion #2 in Section 4.3

  Refractory to last ~~checkpoint inhibitor therapy~~ PD-1/L1 inhibitor-based therapy which is defined as disease progression within 3 months of treatment initiation.

New Text:

- <u>Subjects must have had clinical benefit (stable disease or response) to last PD-1/L1 inhibitor-based therapy for at least three months to be eligible.</u>

Issue #3 – Additional clinical sites will be added to ensure timely enrollment of tumor types planned in the expansion phase

- Synopsis - Planned number of sites section and Section 4.5
  - Text revised to reflect that approximately 8-10 clinical sites may participate in this study

16.13 Summary of Protocol Changes – Amendment 05

The main purpose for this amendment is to revise eligibility criteria and tumor types included for study participation. The dosing window for administration of SL-279252 was clarified in the Schedule of Assessment (SOA) tables.

Minor Editorial Changes:

Document Headers
Updated to denote version 05 of protocol

Title page
Approval date changed to 1 October 2020 and protocol version number changed to version 05

Table of Contents
Updated to include new section on drugs to be used with caution and new Appendix Section 16.13
Page numbers revised

Synopsis
Revised eligibility criteria to align with text changes made in the main body of the protocol as described below.

1) Participant Eligibility Criteria revised as noted below:
   - Revised inclusion criterion #2 in Synopsis and Section 4.2 by removing text that excluded subjects with ocular or uveal melanoma from study participation. Deleted text: ~~Melanoma: Subjects with a diagnosis of uveal or ocular melanoma are excluded.~~
2) Removed enrollment restriction of up to 4 histologies in dose expansion. This change impacted the following sections
   - Description of Study Design in Section 3.1 removed text in the last sentence of the first paragraph as follows: The tumor types for dose expansion ~~(up to 4 histologies)~~ will be determined after review of data collected during dose escalation, and will be selected from the dose escalation list of malignancies.
   - Study Schema in Section 3.1.2 removed dose expansion text ~~Tumor Types: select up to 4 histologies.~~ The legend text to the schema had the following text removed: ~~One to four tumor histologies may be tested in dose expansion.~~
   - Dose Expansion Description in Section 3.3.1 the last sentence in the first paragraph was removed: ~~One to four tumor types (selected from the dose escalation list of malignancies) may be selected for the Dose Expansion Cohorts based on preliminary results from dose escalation.~~
   - Revised inclusion criterion #2 in Synopsis and Section 4.2 by removing text as shown: Subject has a histologically confirmed diagnosis of one of the following unresectable locally advanced or metastatic malignancies: melanoma, non-small cell lung cancer (squamous, adeno, or adeno-squamous), urothelial cancer, squamous cell carcinoma of the head and neck, squamous cell cervical cancer, gastric or gastro-esophageal junction adenocarcinoma, squamous cell carcinoma of the anal canal, squamous cell carcinoma of the skin, renal cell cancer, Hodgkin's lymphoma, and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding CNS malignancies. MSI and MMRD testing results as per institution is acceptable. ~~NOTE: The tumor types for dose expansion (up to 4 histologies) will be determined after review of data collected during dose escalation, and will be selected from this list of malignancies.~~
3) Clarified dosing day windows allowed for administration of SL-279252 in the SOA Tables as follows:

- In SOA 6.1 new text added as footnote n: SL-279252 Administration: SL-279252 should be administered on D1, D8, and D15 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.
- In SOA 6.3 new text added as footnote o: SL-279252 Administration: SL-279252 should be administered on D1, D8, and D15 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.
- In SOA 6.2 new text added as footnote n: SL-279252 Administration: SL-279252 should be administered on D1, D8, D15, and D22 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.
- In SOA 6.4 new text added as footnote o: SL-279252 Administration: SL-279252 should be administered on D1, D8, D15, and D22 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

4) Revised Dose Escalation Plan Table as noted below

- Table 5 Dose Escalation Plan in Section 3.2.4 and as depicted in Synopsis was revised to include windows for duration of infusion of (+/- 10 minutes) for a 30 minute infusion and (+/-15 minutes) for a 1 hour infusion.
    - Footnote e moved as superscript for Duration of Infusion column in Table 5 and text revised as shown (new text in italics):Shorter infusion time may be considered based on final drug volume needed for administration. 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.

5) Revised Footnote o in SOA Tables 6.1 and 6.2 or footnote p in SOA Tables 6.3 and 6.4 on AE Monitoring as shown below

- AE Monitoring:Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started, only SAEs and irAEs that occur *prior to starting the new anticancer therapy* ~~within 30 days from last dose of SL-279252~~ should be recorded. In the event of a continuing SAE or a non-serious irAE, the subject will be asked to return for follow-up until the SAE or irAE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

6) Predose, EOI and 6 hours post EOI PK sample time points were added for collection on C4/D1 to confirm clearance and half-life parameters with repeat dosing of SL-279252. Relevant supplementary PK tables were changed as outlined below.

- Supplementary PK Table 8 in Section 6.1.1, Table 12 in Section 6.1.2, Table 15 in Section 6.3.1 and Table 18 in Section 6.4.1

- Text was added to footnote # 4 in Table 15 in Section 6.3.1 and in Table 18 in Section 6.4.1 stating: C3/D1 and C4/D1 collect a predose sample for PK/ADA and then EOI, and 6 hr post EOI sample for PK.
- Text was updated in Section 6.7.1 as shown below.

  Intensive serial PK samples will be collected for all subjects enrolled in dose escalation cohorts. In the first cycle starting on Day 1, samples will be collected pre-dose, at the EOI, and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours post EOI. Additional PK samples will be collected at 48, 72, and 96 hours post EOI. Actual dose administration and PK sampling times will be documented in the subject's medical record. Sample collection out to 96 hours post EOI may be truncated during dose finding based on emerging data (e.g., lower doses may require collection of PKs only through the 48-hour time point following the first infusion). Subsequently, pre-dose, EOI, 2-hour, 6-hour and 24-hour post EOI samples will be obtained on C1D15/D16 and C2D1/D2. On C3/D1 *and C4/D1*, a pre-dose, EOI, and 6-hour post EOI sample will be collected. Beyond cycle ~~4~~3, only pre-dose samples will be collected for ADA and PK analyses on D1 of ~~C4,~~ C7, C10, C13 and C25. A final PK/ADA sample should be collected within 7 – 30 days after permanently stopping treatment with SL-279252.
- Text was updated in Section 6.7.2

  Sparse PK samples will be collected for all subjects enrolled in Expansion Cohorts. Actual dose administration and PK sampling times will be documented in the subject's medical record. A sample will be collected pre-dose, at the EOI and then 2 and 6 hours after the infusion on C1/D1. A 24-hour post EOI sample will be collected on Day 2 of the first cycle (C1/D2). Subsequently, pre-dose, EOI, 2-hour, 6-hour, and 24-hour post EOI samples will be obtained on C1D15/D16 and C2D1/D2. A predose, EOI and 6-hour post EOI sample will be collected on C3/D1 *and cycle 4/D1*. Beyond cycle ~~4~~3, only pre-dose samples will be collected for ADA and PK analyses on D1 of ~~C4,~~ C7, C10, C13 and C25. A final PK/ADA sample should be collected within 7 – 30 days after permanently stopping treatment with SL-79252.
- Blood Requirements provided in Appendix 16.8 were updated to include additional PK samples added for collection on C4D1

7) Revised wording in Section 7 Safety Assessments as shown below

- Subjects will be followed continuously for AEs starting when a subject has signed the ICF, throughout the course of treatment and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AEs should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started *within 90 days after the last dose of SL-279252*, only SAEs and ~~it~~AEs that occur *prior to starting the new anticancer therapy* ~~within 30 days from last dose of SL-279252~~ should be recorded. All observed or volunteered AEs (serious or non-serious) and abnormal laboratory test findings, if applicable, whether suspected to have a causal relationship to the SL-279252 or not will be recorded in the subject medical record and in the eCRF. AEs will be graded according to NCI-CTCAE v5.0. For all AEs, sufficient information will be pursued and/or obtained to permit an adequate determination of seriousness and outcome of the event (i.e., whether it should be classified as a SAE or not) and an assessment of the causal relationship between the AE and SL-279252. AEs will be followed until resolution (or return to baseline) or stabilization. Refer to Section 7.5 for documentation and reporting of AEs.
  - Revised text in Section 7.5 on Reporting Procedures for AEs in table as shown below to align with wording in Section 7.

Event	Reporting Procedures
Adverse Event	Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from SL-279252 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and

Event	Reporting Procedures
	documented in the eCRF, regardless of whether the event(s) is attributed to trial medication. If another anti-cancer agent is started, only SAEs and AEs that occur *prior to starting the new anticancer therapy* ~~within 30 days from last dose of SL-279252~~ should be recorded. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, and action taken. Follow-up information should be provided as necessary. AEs will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

8) Other minor editorial changes made are noted below (new text added is italicized).

- Duration of Treatment Section 3.11 new text (in italics) added to the last paragraph: Impact of ADA on clinical efficacy (non-response or loss of response to the IP) and safety (product specific immunogenicity risk) will be evaluated *and reported* on an on-going basis *once a validated ADA assay becomes available*. If a subject develops ADA, the Sponsor and investigator may take into consideration these factors in assessing the duration of the therapy.
- Assessment of Severity for AEs is now Section 7.1 moved up and no longer under Section entitled Classification of Adverse Event in Section 7.3 (was Section 7.2 in previous versions of protocol)
    - Section 7 subheadings renumbered to accommodate moving Assessment of Severity Section up and designating it as Section 7.1 in this version of the protocol.
- Removed text from Section 7.4 as shown as shown below.
    - ~~Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity.~~ *The highest grade in severity for each AE will be documented*. AEs characterized as intermittent require documentation of onset and duration of each episode.

16.14 Summary of Protocol Changes – Amendment 06

Minor Editorial Changes:

Document Headers
Updated to denote version 06 of protocol
Title page
Approval date changed to 4 Februrary 2021 and protocol version number changed to version 06
Table of Contents
Updated to include new section on drugs to be used with caution and new Appendix Section 16.14 and revised title header for Section 6.6.6.1
Page numbers revised
Synopsis
Revised exclusion criterion #2 to align with text changes made in the main body of the protocol as described below.
Revised text in Criteria for Dose Limiting Toxicity Section to align with change made in the main body of the protocol as described below

1) Revised exclusion criterion #2 in Section 4.3 to provide an exception for subjects with uveal melanoma
   - New Text shown italics added as a note of clarification: ***Note****: Exclusion criterion #2 and the sub bullet above do not apply to subjects with uveal melanoma.*

2) Clarified language about ad hoc samples to be collected if an infusion-related (IRR) or cytokine release (CRS) adverse reaction occurs.
   - SOA Table 6.1 footnote o. AE Monitoring sub bullet text revised as shown (new text in italics): Ad hoc blood samples for clinical safety labs should be collected for ~~S~~AE related to IRR *and/*or CRS events as noted in Section 6.6.6.1 and the SLM
   - SOA Tables 6.2 footnote o, 6.3 and 6.4 footnote p AE Monitoring sub bullet text revised as shown (new text in italics): Ad hoc blood samples for clinical safety labs should be collected for ~~S~~AE *related to IRR and/or CRS events* ~~related to infusion or CRS events~~ as noted in Section 6.6.6.1 and the SLM.
   - Section 6.6.6.1 Section title and text revised as show (new text in italics): Title revision; Ad Hoc Labs for ~~S~~*AEs of IRR and/or CRS* and text revision; Ad hoc labs should be collected as noted if IR*R and/or* CRS *events* ~~or an immune-related adverse event (irAE)~~ occur~~s~~. The samples to be collected are provided below.
   - Section 7.2 Table section defining Laboratory test(s) tha meet definitions of an AE or SAE; text revised in sub bullet #2 as follows (new text shown in italics): • Ad hoc labs should be collected as noted in Section 6.6.6.1 above if *AEs of* IRR *and/or /*CRS ~~or an irSAE~~ occur~~s.~~

3) Clarified language about the DLT-evaluable population for subjects receiving SL-279252 therapy.
   - Section 3.2.6 last paragraph in section revised as shown: A Grade ≥ 3 AE that occurs beyond the DLT period (21 days for schedule 1 or 28 days for schedule 2) or Grade 2 events that require continuous interruption of SL-279252 for more than 6 weeks or

toxicities that result in subjects not receiving at least *66*~~50~~% of the scheduled dose during the DLT assessment period may be taken into consideration when assessing the totality of the data in determining evaluability for DLT and the RP2D.

Section 9.3 in the table that includes populations for Analyses the DLT Evaluable population is defined as (new text in italics): All subjects in the All Treated population who receive at least 2 doses of SL-279252 *for Schedule 1 or at least 3 doses for Schedule 2*, 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. Evaluable subjects will be used to guide dose escalation and to determine the MTD or MAD.

16.15 Summary of Protocol Changes – Amendment 07

Minor Editorial Changes:

Document Headers

Updated to denote version 07 of protocol

Title page

Approval date changed to 12 July 2021 and protocol version number changed to version 07

Rational for Global Amendment 06

Minor editorial changed noting summary provided for Amendment 06 ~~05~~

Rational for Global Amendment 07 added

Abbreviations list

Added TPS and CPS to abbreviations list

Table of Contents

Updated to include new Appendix Section 16.15

Page numbers revised

Synopsis

Revised inclusion criterion #2 to align with text changes made in the main body of the protocol as described below.

Added new inclusion criterion #3 to align with text changes made in main body of the protocol as described below.

Revised exclusion criterion #2 to align with text changes made in main body of the protocol as described below

1) Institute requirement that eligible subjects have tumors with PD-L1 expression ≥1% according to tumor TPS or CPS at baseline.

- Section 1.3 Rationale; new text (italics) added as shown below:

  This first-in-human Phase 1 study will evaluate the safety, tolerability, PK, anti-tumor and pharmacodynamic effects of SL-279252 to identify the dose and schedule i.e., recommended Phase 2 dose (RP2D) for future development. The trial will enroll patients with tumor types that have demonstrated benefit from anti-PD1/L1 inhibitor therapy i.e., melanoma, non-small cell lung cancer (NSCLC), urothelial cancer, head and neck squamous cell carcinoma (HNSCC), squamous cell cervical cancer, gastric or gastro-esophageal junction (GEJ) adenocarcinoma, squamous cell carcinoma of the anal canal (SCCA), squamous cell carcinoma of the skin (Skin-SCC), renal cell cancer (RCC), Hodgkin's lymphoma (HL), and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding central nervous system (CNS) malignancies. *Given that SL-279252 likely requires binding of PD-L1 to mediate activity within the tumor, the study was amended to require eligible subjects to have tumors with PD-L1 expression ≥1% by tumor proportion score (TPS) or combined proportion score (CPS) at baseline*.

- Section 4.2 Inclusion Criteria; new text (italics) added as criteria #3 shown below:

  3. *Eligible subjects must have tumors expressing PD-L1 ≥1% by tumor proportion score (TPS) or combined proportion score (CPS) as determined by a local laboratory.*
     - *This criteria does not apply to subjects with a diagnosis of melanoma, renal cell carcinoma, Hodgkin's lymphoma and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors.*

- SOA tables 6.1, 6.2, 6.3 and 6.4 new text (italics) added to footnote a in all of these tables in reference to Screening as shown:

  Subjects will be enrolled based on local PD-L1 tumor testing results. Any PD-L1 tumor testing results prior to enrollment are acceptable.

2) Subjects with uveal or ocular melanoma are ineligible for participation.
   - Section 4.2 Inclusion Criterion #2; new text (italics) added as shown below:
     2. Subject has a histologically confirmed diagnosis of one of the following unresectable locally advanced or metastatic malignancies: melanoma, non-small cell lung cancer (squamous, adeno, or adeno-squamous), urothelial cancer, squamous cell carcinoma of the head and neck, squamous cell cervical cancer, gastric or gastro-esophageal junction adenocarcinoma, squamous cell carcinoma of the anal canal, squamous cell carcinoma of the skin, renal cell cancer, Hodgkin's lymphoma, and microsatellite instability high (MSI-H) or mismatch repair deficient (MMRD) solid tumors excluding CNS malignancies. MSI and MMRD testing results as per institution is acceptable.
        - Head and neck cancers: Subjects must have primary tumor locations in the oropharynx, oral cavity, hypopharynx, or larynx. Primary tumor sites of nasopharynx, maxillary sinus, paranasal, and unknown primary are excluded.
        - Non-small cell lung cancers: Subjects with a known EGFR sensitizing (activating) mutation or an ALK fusion are excluded.
        - *Melanoma: Subjects with a diagnosis of uveal or ocular melanoma are excluded.*

   - Section 4.3 Exclusion Criterion #2; text deleted as shown:
     2. Refractory to last PD-1/L1 inhibitor-based therapy which is defined as disease progression within 3 months of treatment initiation.
        - Subjects must have had clinical benefit (stable disease or response) to last PD-1/L1 inhibitor-based therapy for at least three months to be eligible.

        ~~**Note**: Exclusion criterion #2 and the sub-bullet above do not apply to subjects with uveal melanoma.~~

3) Removed reference to 1 mL fill size of drug product to allow for larger fill volume.
   - Section 5.1 Investigational Product Description; edited text as below:

     Unit dose strength(s)/Dose Level(s):

     20 mg/mL; ~~1.0 mL~~ in a ~~10 mL sized~~ *glass* vial (Refer to Section 3.2.4 for dose levels). *Refer to the Study Pharmacy Manual (SPM) for further description of drug product.*
   - Section 5.2.1 Preparation

   SL-279252 solution for infusion, 20 mg/mL is supplied as a frozen liquid. Before use, thaw each vial of SL-279252 for infusion (20 mg/mL~~, 1mL~~) overnight under refrigerated conditions protected from light or at room temperature *until completely thawed to a clear solution* ~~over 1 hour~~.

4) Minor editorial changes were made to clarify study conduct procedures during dose escalation and requirements for collection of ad hoc labs if IRR and/or CRS occur.
   - New text (in italics) added to the 1st paragraph in Section 3.1 Description of the Study Design as shown below:

This is a Phase 1 first in human, open label, multi-center, 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. The tumor types selected have been reported in the literature to be responsive to PD-1/L1 inhibitors. 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. *A subset of one or more selected tumor type(s) from the list of eligible histologies may be identified for enrollment in dose escalation*. 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.

- Minor editorial change made to 1st sentence in Section 6.6.6.1 as shown:

  Ad hoc labs should be collected as noted if IRR and/or CRS ~~events or an immune-related adverse event (irAE)~~ occur. The samples to be collected are provided below.