CLINICAL DEVELOPMENT APPROVAL PAGE

Protocol No.	SI-B037-ST-101	
Title:	SI-B037-ST-101: A Multicenter, Open-Label, Phase 1/1b, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of SI-B037 in Adult Patients with Advanced/Metastatic Solid Tumors That Are Refractory to Standard Therapies	
Investigational Products:	SI-B037	
Regulatory Agency Identifiers	US FDA IND	179441
	ClinicalTrials.gov	TBD
	Eudra CT No.:	TBD
Version:	V2.0	22 September 2026
Replaces:	V1.0	10 August 2026
Sponsor:	SystImmune, Inc.	

Clinical Development Approval:

Signed by:
Giuseppe Russo
Signer Name: Giuseppe Russo
Signing Reason: I approve this document
Signing Time: 9/23/2026 | 10:08:31 AM PDT
5F1D61BECD724E29A09E8FA9279DC041

9/23/2026

Giuseppe Russo, PhD
Executive Director - Clinical Development,
SystImmune, Inc.

Date

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INVESTIGATOR AGREEMENT PAGE

SystImmune, Inc.

SI-B037
22 Sept 2026

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

Principal Investigator	**Date**

Printed Name:

Institution:

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TITLE PAGE

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Full Title:	SI-B037-ST-101: A Multicenter, Open-Label, Phase 1/1b, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of SI-B037 in Adult Patients with Advanced/Metastatic Solid Tumors That Are Refractory to Standard Therapies
Trial Acronym:	SI-B037-ST-101
Sponsor Protocol Identifier:	SI-B037-ST-101
Version Number:	2.0
Date	22 Sept 2026
Amendment Identifier:	1
Amendment Date:	22 Sept 2026
Amendment Scope:	N/A
Sponsor's Investigational Product Code(s):	SI-B037
Investigational Product Name(s):	N/A
Phase of Development:	1/1b

Short Title:	A Multicenter, Open-label, Phase 1/1b, Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of SI-B037 in Solid Tumors	
Sponsor:	SystImmune, Inc. 902 Carnegie Center Blvd Princeton, NJ 08540	
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Compliance Statement		
This study will be conducted in accordance with the laws, regulations, and guidelines established by local and regional authority(ies). In addition, this clinical trial will be conducted in compliance with the International Conference on Harmonisation (ICH) E6 R2 and Guidelines for Good Clinical Practice. Study documents will be maintained in accordance with applicable regulations.		

DOCUMENT HISTORY

Document	**Date**
Original Protocol	10 Aug 2026
Amendment 1	22 Sept 2026

SUMMARY OF CHANGES

Section	Change	Rational
Global	Editorial changes	Removed typographical and formatting errors
Section 1.3 Table 1	Table 1 footnote f updated to change tumor imaging evaluation from every 8 weeks to every 6 weeks in the first year after the safety visit Footnote g updated to clarify that no IO-naïve NSCLC testing for PD-L1 is required before enrollment.	Increased frequency to more actively monitor disease progression by imaging Improved footnote g text to align with updated inclusion criteria
Section 1.3, Table 1 footnote w and footnote x, and Section 8.5.1	Changed duration of time TEAEs, AESI and TRSAE will be collected	Updated to more accurately reflect current requirements for safety analysis
Section 1.3 Table 2	Added additional time points to Cycle 4 EOI assessments	Add additional PK time points at steady-state
Section 1.3 Table 2 and Table 3	Note added to Table 2 and Table 3 indicating that the end of infusion time point is after a post infusion saline flush	Added note to clarify timing in sample collection
Synopsis, Sections 4.1.1, 4.1.2 and 4.1.2.5	Text updated to clarify that the starting doses for dose expansion (Part C) will be selected based on the totality of evidence including PK, PD, safety, tolerability, and activity	Text updated at the request of FDA reviewer
Sections 4.1.2, and 9.3.4	Text updated to clarify number of subjects in Dose Finding	Correct error as original sentence contained dose escalation in when this sentence only applies to dose finding
Section 4.1.3	Text added to indicate the futility analysis will be performed for each Dose Expansion cohort	Futility analysis added at request of FDA reviewer
Synopsis, Section 5.1	Inclusion Criterion #4 has been updated	Clarified criteria to be considered failing 1 line of therapy
Synopsis, Section 5.1	Inclusion Criterion #5 has been added	Criterion added to clarify participants should have at least one measurable lesion
Synopsis, Section 5.1	Inclusion Criterion #9 has been updated	Criterion has been updated to remove participants with liver metastasis with a TBIL greater than 1.5 x ULN
Synopsis, Section 5.1	Inclusion Criterion #12 has been added	Criterion added at the request of FDA reviewer
Synopsis, Section 5.1	Inclusion Criterion #13 has been updated	Criterion updated at the request of FDA reviewer
Synopsis, Section 5.1	Inclusion Criterion #14 has been updated	Improved description of participants to be enrolled in the IO naïve NSCLC cohort
Synopsis, Section 5.1	Inclusion Criterion #15 has been updated	Criterion updated at the request of FDA
Synopsis Section 4.3.6	Dose-Limiting Toxicities have been updated	Updated to use lab values instead of Grades when defining DLT criteria for neutrophil and platelets related adverse events; updated rules for infusion related reactions; added rule for AST/ALT; added rules exceptions for amylase and rash

Section 6.6, Table 9	Revise neutropenia and thrombocytopenia dose modification guidelines in Table 9 to include lab values in () after Grade	Modifications were made in response to a recommendation by FDA reviewer
Section 7.1	Changed timing from 6 weeks to 21 days for participants discontinuation after dose interruption	Change made at the request of FDA reviewer
Section 8.1	Text added to clarify that tumor tissue for all participants will be collected for retrospective analysis	Updated to further clarify that tumor tissue will be used for retrospective biomarker analysis
Section 9.4	Added an interim analysis to assess treatment futility	Change made at the request of FDA reviewer
Appendix 9	Text added to clarify the following: Crossing a boundary will not automatically result in an enrollment pause; Decisions regarding ongoing enrollment will be based on the totality of available evidence and the overall benefit-risk profile	Change made at the request of FDA reviewer

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
AUC_0	area under the curve from time zero to infinity
AUC_{0-8}	area under the serum concentration-time curve from time 0 to 8 hours
AUC_{last}	area under the serum concentration-time curve up to the last quantifiable time
BC	breast cancer
BCRP	breast cancer resistance protein
bFGF	basic fibroblast growth factor
BMT	Bayesian toxicity monitoring
BOIN	Bayesian optimal interval
BRCA	breast cancer gene
BTC	biliary tract cancer
CBC	complete blood count
CC	cervical cancer
CCA	cholangiocarcinoma
CDC	complement dependent cytotoxicity
CIT	chemotherapy-induced thrombocytopenia
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
ConMeds	concomitant medications

Abbreviation or Term	Definition/Explanation
CPI	checkpoint inhibitor
Cr	creatinine
CR	complete response
CRC	colorectal cancer
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
D1Q3W	Day 1 every 3 weeks
DCR	disease control rate
DE	dose elimination
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose-limiting toxicity
DOR	duration of response
EC	endometrial cancer
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
EV	enfortumab vedotin
Fc	Fragment crystallizable region
FDA	Food and Drug Administration
FcγR	Fc gamma receptor
FFPE	formalin-fixed paraffin-embedded
FN	febrile neutropenia
FSH	follicle stimulating hormone
G-CSF	granulocyte colony-stimulating factor

Abbreviation or Term	Definition/Explanation
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
Hb	hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICI	immune checkpoint inhibitor
ICF	informed consent form
IgG1	Immunoglobulin G1
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
IND	Investigational New Drug
IFN	interferon
INR	International Normalized Ratio
IP	investigational product
IO	Immuno-Oncology
irAEs	Immune-related Adverse Events
IOCBP	Individuals of childbearing potential IOCBP
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
IRR	infusion-related reaction
ISH	in situ hybridization
IV	intravenous
K_{el}	terminal elimination rate constant
LLOQ	lower limit of quantitation
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MABEL	minimal anticipated biological effect level
MAD	maximum administered dose
MDSC	myeloid-derived suppressor cell

Abbreviation or Term	Definition/Explanation
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSED	minimum safe and pharmacologically effective dose
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NPACT	non-protocol anticancer therapy
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	non-small cell lung cancer
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PARP	poly ADP ribose polymerase
PBC	platinum-based chemotherapy
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PE	physical exam
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic
PLT	platelet
PO	orally
PR	partial response
PS	performance status
Q3W	every 3 weeks
QA	quality assurance

Abbreviation or Term	Definition/Explanation
QTcF	QT interval corrected (Fridericia formula)
RBC	red blood cell
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RSI	reference safety information
RTK	receptor tyrosine kinases
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
scFv	single-chain variable fragment
SD (nonclinical)	Sprague Dawley rats
SD (clinical)	stable disease
SD (statistical)	standard deviation
SMC	Safety Monitoring Committee
SoC	standard of care
SOC	system organ class
SOP	standard operating procedures
$t_{½}$	elimination half-life
TAB	total antibody
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TdP	Torsades de Pointes
TNF	Tumor Necrosis Factor
TRAE	treatment-related adverse event
T_{max}	time to maximum concentration
TME	Tumor microenvironment
TNBC	triple-negative breast cancer
TTR	time to response
UC	urothelial cancer
UPC	urine protein/creatinine
ULN	upper limit of normal
VEGF	Vascular Endothelial Growth Factor
VEGF-A	Vascular Endothelial Growth Factor A

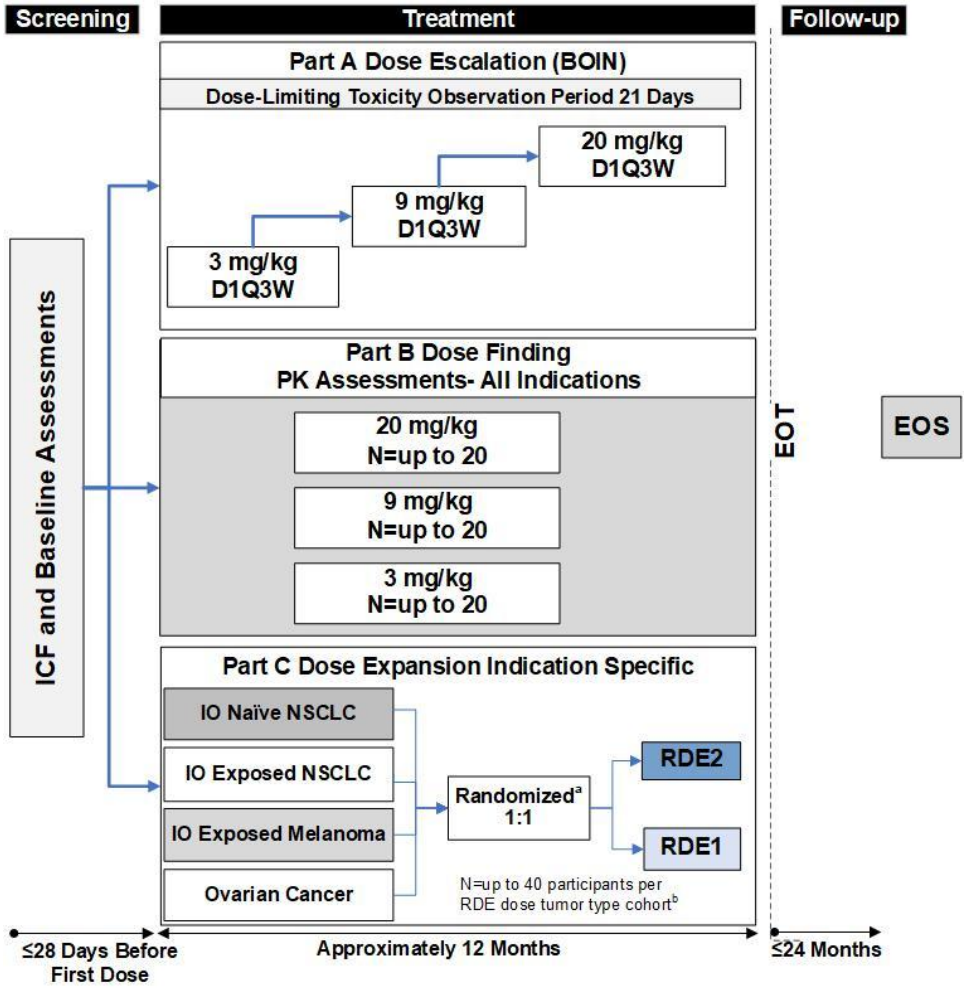
Abbreviation or Term	Definition/Explanation
VEGFR-2	Vascular Endothelial Growth Factor Receptor 2
V_{ss}	apparent volume of distribution at steady-state after multiple doses
V_z	volume of distribution after a single dose
WBC	white blood cell
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1.1. Protocol Synopsis

Study Title	SI-B037-ST-101: A Multicenter, Open-Label, Phase 1/1b, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of SI-B037 in Adult Patients with Advanced/Metastatic Solid Tumors That Are Refractory to Standard Therapies
Protocol Number	SI-B037-ST-101
Investigational Product	SI-B037
Target Population	Part A and Part B: The target population includes participants with locally advanced/metastatic tumors. Part C: non-small cell lung cancer (NSCLC), ovarian cancer, melanoma, and other solid tumors
Phase of Development	Phase 1/1b
Study Centers Planned	Approximately 50 sites in the United States and Canada. Additional sites and countries may be added as needed.
Estimated Study Enrollment Duration	**Dose Escalation** • Approximately 6 months for enrollment • Approximately 12 months for treatment and follow-up **Dose Finding** • Approximately 9 months for enrollment • Approximately 12 months for treatment and follow-up **Dose Expansion** • Approximately 18 months for enrollment • Approximately 12 months for treatment and follow-up
Estimated Participant Duration	It is estimated that subjects will participate for an average of 12 months on study treatment per stage of the study. Subjects will be followed until death, withdrawal of consent, or sponsor decision to no longer collect survival data.
Trial Design	This study is an open-label, multicenter, first-in-human (FIH) clinical trial designed to evaluate the safety, tolerability, pharmacokinetic (PK) characteristics, and preliminary efficacy of SI-B037 in participants with locally advanced or metastatic solid tumors. This study has 3 parts: Part A-dose escalation Part B-dose finding Part C-dose expansion The starting doses for dose expansion (Part C) will be selected based on the totality of evidence including PK, PD, safety, tolerability, and activity.obtained from dose escalation and dose findings (Part A and Part B respectively), which has the objective to identify a safe and effective recommended Phase 2 dose (RP2D). Additional intermediate doses may be added based on emerging data. A high-level schema of Study SI-B037-ST-101 is shown in Figure S1.

Figure S1: High-level Schema of Study SI-B037-ST-101



Abbreviations: BOIN=Bayesian Optimal Interval; D1Q3W=day 1 every 3 weeks; EOS=end of study; EOT=end of treatment; ICF=informed consent form; IO=Immuno-oncology; OC=ovarian cancer; NSCLC=non-small cell lung cancer; PK=pharmacokinetics; RDE= recommended dose for expansion

a. Participants for each tumor cohort will be randomized to receive either RDE1 or RDE2

b. Up to 80 participants per tumor type (up to 40 per RDE dose) will be randomized to receive SI-B037 at either RDE1 or RDE2

*Note: RDE1 is the lower dose that will be chosen for expansion, also known as Dose -1. RDE2 will be the RP2D and the higher dose chosen for expansion.

Part A: Dose Escalation

Beginning with Cycle 1, SI-B037 will be administered by intravenous (IV) infusion on Day 1 every 3 weeks (D1Q3W) (Table S1):

Table S1: Dose Escalation Doses

Dose Level	Day 1 Dosage (D1Q3W) [a] (21-day cycles)
1	3 mg/kg
2	9 mg/kg
3	20 mg/kg

Abbreviations: D1Q3W=Day 1 every 3 weeks (1 cycle); IV=intravenous; PK=pharmacokinetic.

a. Intermediate doses may be considered based on review of available safety, tolerability, and PK data in this and other studies with the investigational product.

Dose Escalation Design

Dose escalation will begin with a BOIN design as described in Section 4.2.3 and proceed until the maximum tolerated dose (MTD) or minimum safe and pharmacologically effective dose (MSED) is reached:

The dose-limiting toxicity (DLT) observation period is defined as the initial 21 days of Cycle 1. A DLT-evaluable participant is defined as a participant who has received at least 1 dose of SI-B037 and has either completed the DLT observation period or experienced a DLT during the DLT observation period. In dose escalation, participants who are not DLT-evaluable will be replaced.

Recommended dose(s) for Part C/dose expansion (RDE) candidate will be selected by the sponsor in collaboration with the Safety Monitoring Committee (SMC) composed of study investigators and sponsor representatives based on a cumulative review of all available treatment-emergent data, that may include safety, tolerability, PK, and pharmacodynamic (PD)/biomarker data from each dose cohort.

Bayesian Optimal Interval (BOIN) Design

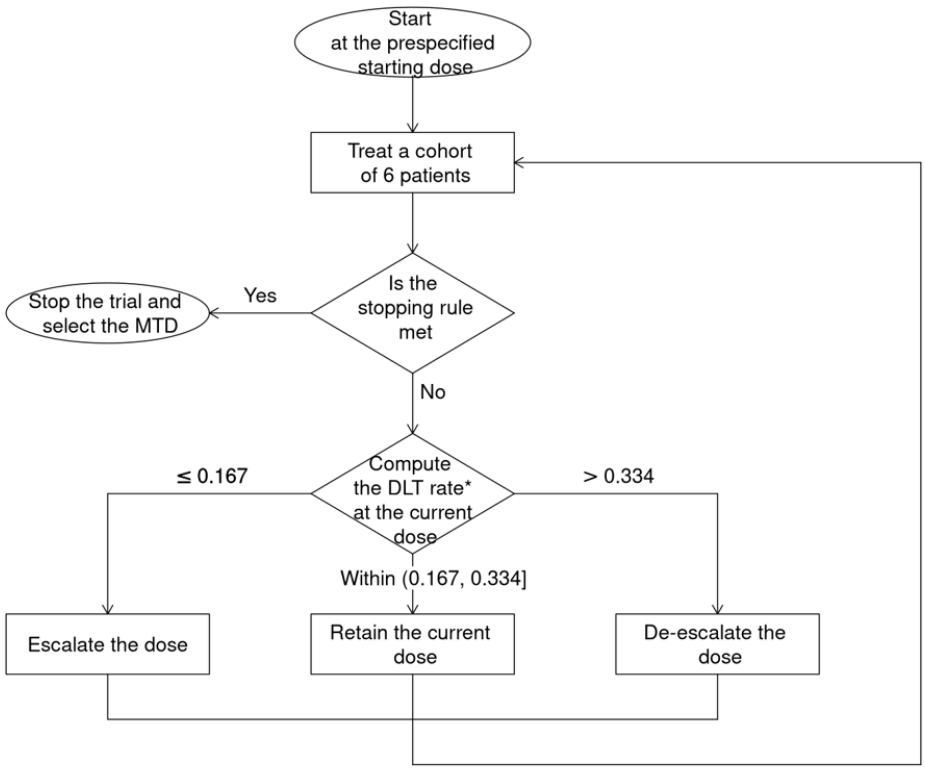
Dose escalation will be guided by the BOIN design to find the MTD based on observed DLTs (Liu and Yuan 2015; Yuan et al. 2016). The computation is implemented by the software "BOIN" available at http://www.trialdesign.org. The target toxicity rate for the MTD is $\phi = 0.25$ and the sample size is approximately 18 DLT-evaluable participants. The BOIN design uses the following rule, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.167, escalate the dose to the next higher dose level;
- If the observed DLT rate at the current dose is > 0.334, de-escalate the dose to the next lower dose level;
- Otherwise, stay at the current dose.

The rule is optimized to minimize the probability of incorrect dose assignment under alternative hypotheses $\phi_1 = 0.1$ (underdosing) and $\phi_2 = 0.43$ (overdosing). The decision-making flowchart for escalation (E), staying (S) at the current dose, dose de-escalation (D) to the previous or an intermediate dose, and dose de-escalation with dose elimination (DE) of current and higher doses, based on the number of participants treated and the number of toxicities (DLTs) observed at a given dose level is provided in Figure S2 The decision will be made by the sponsor in collaboration with the SMC (Section 4.2.5) according to the BOIN escalation rules (Section 4.2.3).

Participants will be enrolled and treated in cohorts of 3 to 6 participants during the dose escalation part. The dose escalation will stop if the number of participants treated at the current dose reaches 12 and the decision by the sponsor and SMC according to Figure S2 is to retain the current dose. After the dose escalation part is completed, the MTD is determined based on isotonic regression, and the MTD is selected as the dose where the isotonic estimate of the toxicity rate is closest to the target toxicity rate (Liu and Yuan 2015). If there are ties, the higher dose level will be selected when the isotonic estimate is lower than the target toxicity rate and the lower dose level will be selected when the isotonic estimate is greater than or equal to the target toxicity rate.

Figure S2: BOIN Design Escalation Flowchart



$$\text{* DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose.

Dose-Limiting Toxicities

The DLT observation period is the first cycle of treatment (21 days) at each dose level. Toxicities will be graded for severity according to the Common Terminology Criteria for Adverse Event (CTCAE v6.0). Primary prevention of diarrhea, nausea, and vomiting is allowed during the DLT observation period as described in Section 6.9.3.

A DLT is defined as any of the following events that are not clearly due to the underlying disease, disease progression, or extraneous causes:

- Any TEAE of ≥ Grade 3 except those that are clearly and incontrovertibly due to disease progression or extraneous cause.
- Toxicity that results in a >14-day delay in treatment.
- **Hematologic toxicities:**

  ANC <500/mm³ (<0.5×10⁹/L) lasting >7 days

  Febrile neutropenia of any grade and any duration

  Platelets <50,000-25,000 mm3 with significant bleeding or platelets <25,000 mm3 for more than 7 days

  Grade 4 thrombocytopenia lasting >72 hours.

- **Non-hematologic toxicities:**

Death not related to disease progression or extraneous cause.

Hy's law cases.

Grade 3 or higher infusion-related reactions (IRR) except for a first occurrence of Grade 3 IRR that occurs in the absence of steroid prophylaxis and resolves within 6 hours following appropriate clinical management

AST/ALT 5–8× ULN persisting >2 weeks, both regardless of presence of liver metastases.

Grade ≥3 non-hematologic toxicities, **except for**:

- Grade ≥3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care;
- Grade ≥3 fatigue for less than 1 week;
- Grade ≥3 electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions;
- Grade 3 amylase or lipase not associated with symptoms/manifestations of pancreatitis and does not require hospitalization.
- Grade 3 rash that improves to Grade <3 with standard management within 7 days

No delay in dosing or dose adjustment will be allowed during the DLT observation period unless clinically indicated.

Part B: Dose Finding

In the dose finding part of the study, approximately 60 participants may be enrolled (3 to 20 participants at each single dose level). However, the actual number of participants enrolled depends on the numbers of dose levels studied, any expansions within a dose level, and any participant replacement required to complete a dose level.

After each dose level completes its individual DLT observation period and the sponsor in collaboration with the SMC determines that further dose escalation is safe, the study will proceed to the dose finding phase. In this phase, up to 20 participants will be treated at each dose of 3 mg/kg, 9 mg/kg, or 20 mg/kg candidate recommended dose for expansions (RDE). The objective of dose finding is to confirm the tolerability of SI-B037 at these candidate RDEs.

Guidelines for dose modifications such as dose reductions, delays, and permanent discontinuations are provided in Section 6.6.

During the dose finding, enrollment will be carefully monitored based on the occurrence of TRAEs that meet DLT criteria for each selected RDE candidate. The incidence and nature of TRAEs observed at each dose level during the dose finding part will be evaluated as part of the overall benefit-risk assessment. The sponsor, together with the SMC, will review the safety data and may determine that an RDE candidate is not tolerable.

Enrollment may be stopped at that dose level, and a lower dose will be selected for further exploration in Part C. This gating mechanism ensures that only doses that demonstrate an acceptable safety profile and tolerability are continued in the study, safeguarding the well-being of the enrolled participants.

Part C: Dose Expansion

After each dose level completes its individual DLT observation period and the sponsor and the SMC determines that further dose escalation is safe, the study will proceed to Part C. Upon

	completion of dose escalation and, when applicable, dose finding, dose expansion will begin, with the objectives to (1) confirm the safety of SI-B037 at the RDEs, (2) evaluate preliminary efficacy in participants with locally advanced or metastatic tumors, and (3) determine the dose that shows the best risk-benefit balance. The doses for this cohort, RDE1, and RDE2, will be selected by the sponsor and the SMC based on the totality of available data. Participants will be assigned as follows: Participants will be selected based on their tumor type and then randomized into 1 of 2 dose cohorts. Up to 40 participants may be enrolled in each dose cohort within each tumor type, for a total of up to 80 participants per tumor type. Participants will be treated in the following manner: SI-B037 dose level: (1) RDE1 or (2) RDE2 D1Q3W and into each of the following sub-cohorts: a) IO-Naïve NSCLC b) IO-Exposed NSCLC c) IO-Exposed melanoma d) Ovarian cancer **Dose Rationale** This study will determine the MTD (if reached), maximum administered dose (MAD), and RDE. Dose levels have been selected based on the results of in vitro antitumor activity, targeted occupancy results from preclinical pharmacology, as well as clinical experience with PD-1 and VEGF pathway inhibition, and the biological rationale for combined PD-1 and VEGF pathway modulation. **Starting Dose (Dose Level 1: 3 mg/kg)** The starting dose for FIH administration will be 3 mg/kg, corresponding to a traditional and clinically efficacious PD-1 inhibitor dose level. Although this dose is below the calculated minimal anticipated biological effect level (MABEL) for SI-B037, it was selected to provide an additional safety margin for FIH evaluation while remaining within a dose range with substantial clinical experience for PD-1 and VEGF pathway inhibition. Given the well-characterized safety profile of the PD-1/VEGF inhibitor class and the advanced oncology population enrolled in this study, initiating dose escalation at 3 mg/kg is considered an appropriate and scientifically justified approach. The selected starting dose is further supported by extensive clinical data demonstrating pharmacodynamic target engagement and antitumor activity of PD-1/VEGF inhibition at comparable dose levels. **Second Dose Level (Dose Level 2: 9 mg/kg)** The second dose escalation level will approximate the clinically established dose range of bevacizumab (anti-VEGF-A therapy). Escalation to this dose is designed to explore enhanced VEGF pathway modulation while maintaining overlap with known safety and tolerability profiles of anti-angiogenic therapy. This dose level allows evaluation of incremental biological activity beyond PD-1–dominant effects and supports characterization of PK/PD relationships relevant to VEGF-A inhibition. **Third Dose Level (Dose Level 3: 20 mg/kg)** The third dose escalation level will target combined PD-1 and VEGF pathway engagement at a higher exposure level (20 mg/kg). This dose is intended to maximize dual-pathway biological activity and to assess the upper range of tolerability for combined immunomodulatory and anti-angiogenic effects. Escalation to this level will proceed only after reviewing cumulative safety, PK, and PD data from prior dose levels, in accordance with protocol-defined escalation criteria. Dose escalation will follow a standard cohort-based approach, with decisions guided by observed DLTs, overall safety profile, and emerging PK/PD data. **Data Collection**

<table>
<tr><td></td><td>Data will be collected at the site in the electronic case report form (eCRF) as indicated in the schedule of assessments and as needed. Detailed data collection and the assessment schedule are provided in Schedule of Activities (SOA) Section 1.3.
End of Treatment
The end of treatment is reached when a participant experiences disease progression, an intolerable toxicity, or is terminated due to other reasons (e.g., withdrawal of consent or death).
End of Study
The end of study is defined as the date when all participants have completed the final protocol-specified safety assessments and/or discontinued study participation (withdrawal of consent or lost to follow-up), whichever occurs first.</td></tr>
<tr><td>Inclusion Criteria</td><td>Participants must meet all the following inclusion criteria to be eligible for participation in this study:
1. Signed the informed consent form voluntarily and agreed to follow the trial requirements.
2. Male or Female Age ≥18 years.
3. Has a life expectancy of ≥3 months.
4. Subjects with documented locally advanced or metastatic solid tumor(s) not amenable to curative surgery or radiation and have received at least 1 line of standard therapy in the metastatic setting, or whose cancer is considered refractory to the SoC or for which no standard treatment is available.
Participants with recurrence or progression occurring during or ≤6 months after completion of neoadjuvant/adjuvant systemic therapy would be considered as having failed 1 line of standard therapy in the metastatic setting and hence be eligible for the trial.
5. At least 1 measurable lesion based on RECIST v1.1
6. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1.
7. Toxicity of previous antitumor therapy has returned to level ≤1 as defined by NCI-CTCAE V6.0 (except for asymptomatic laboratory abnormalities such as elevated ALP, hyperuricemia, elevated serum amylase/lipase, and elevated blood glucose; except for toxicity that the investigator determined to have no safety risk, such as alopecia, Grade 2 peripheral neurotoxicity, hypothyroidism stabilized by hormone replacement therapy, etc.).
8. Has no serious cardiac dysfunction and left ventricular ejection fraction ≥50%.
9. Has adequate organ function, before enrollment defined as:
<table>
<tr><th>System</th><th>Lab Value</th></tr>
<tr><td>Hematological[a]</td><td></td></tr>
<tr><td>Absolute neutrophil count (ANC)</td><td>≥1.5 ×10^9/L</td></tr>
<tr><td>Platelets</td><td>≥100×10^9/L</td></tr>
<tr><td>Hemoglobin (Hb)</td><td>≥9.0 g/L</td></tr>
<tr><td>Hepatic[b]</td><td></td></tr>
<tr><td>Total bilirubin (TBIL)</td><td>≤1.5× upper limit of normal (ULN)
≤3×ULN for participants with Gilbert’s syndrome</td></tr>
<tr><td>AST and ALT</td><td>≤2.5×ULN without liver metastasis
≤5.0×ULN with liver metastasis</td></tr>
<tr><td>Renal[c]</td><td></td></tr>
<tr><td>Creatinine clearance (CrCl)</td><td>≥50 mL/minute</td></tr>
<tr><td>Urine protein</td><td>≤2+ OR ≤1000 mg/24 hours</td></tr>
<tr><td>Coagulation[d]</td><td></td></tr>
<tr><td>International Normalized Ratio (INR)</td><td>≤1.5×ULN</td></tr>
</table></td></tr>
</table>

	Activated partial thromboplastin time (aPTT) ≤1.5×ULN

a. Blood transfusion, platelet transfusion, erythropoietin (EPO), hematopoiesis agents (such as [TPO]), and G-CSF use are not allowed 1 week prior to Screening.

b. For participants with Gilbert's syndrome, conjugated bilirubin ≤1.5×ULN and TBIL ≤3.0×ULN.

c. Creatinine clearance (Cockcroft-Gault equation).

d. Unless receiving anticoagulation therapy with PT and aPTT levels within the intended therapeutic range.

10. Sexually active fertile participants and their partners must agree to use highly effective methods of contraception (defined in Appendix 5 of the protocol) during the course of the study and for 4 months for men and 7 months for women after the last dose of study treatment. An additional contraceptive method, such as a barrier method (e.g., condom), is recommended.
11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at Screening and must be nonlactating. Female participants are considered WOCBP unless one of the following criteria are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman >45 years old in the absence of other biological or physiological causes. In addition, females <55 years old must have a serum follicle stimulating hormone (FSH) level >40 mIU/mL to confirm menopause.

    NOTE: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

12. Participants whose tumor has an actionable biomarker(s) for which an US FDA or other country-specific approved targeted therapy exists in the applicable disease setting must have previously received the appropriate targeted therapy and experienced disease progression during or after treatment, unless such therapy was contraindicated, not tolerated, unavailable, inaccessible, or otherwise not considered medically appropriate by the Investigator.

PART C Additional Inclusion Criteria (Dose Expansion Only)

For IO-exposed NSCLC:

13. Histologically or cytologically confirmed unresectable locally advanced or metastatic NSCLC in subjects previously exposed to immune checkpoint inhibitor therapy (IO-exposed), defined as having received at least one prior line of treatment with a PD-1 inhibitor, and/or PD-L1 inhibitor, and/or CTLA-4 inhibitor in combination with a PD-1 inhibitor, and/or other approved immune checkpoint–modulating agents (as monotherapy or in combination), and whose disease is refractory to SoC therapy or for whom no appropriate standard treatment options are available. In addition, subjects must have received at least one prior line of platinum therapy.

For IO-Naïve NSCLC:

14. Histologically or cytologically confirmed unresectable locally advanced or metastatic NSCLC in subjects with no prior exposure to immune checkpoint inhibitor therapy (IO-naïve), defined as having no prior treatment with a PD-1 inhibitor, PD-L1 inhibitor, CTLA-4 inhibitor, or other approved or investigational immune checkpoint–modulating agent (as monotherapy or in combination). In addition, subjects may have received one prior line of platinum

	therapy +/-anti-VEGF Mab for locally advanced or metastatic NSCLC and failed the treatment. **For Melanoma:** 15. Histologically confirmed unresectable or metastatic melanoma with prior treatment with an immune checkpoint inhibitor therapy (IO-exposed), including a PD-1 inhibitor, and/or PD-L1 inhibitor, and/or CTLA-4 inhibitor in combination with a PD-1 inhibitor, and/or other approved immune checkpoint–modulating agents (as monotherapy or in combination) and documented disease progression following such therapy. **For Ovarian Cancer:** 16. Has histologic documentation of epithelial ovarian, primary peritoneal, or fallopian tube cancer that has progressed or relapsed on or after a previous chemotherapy with or without a poly ADP ribose polymerase (PARP) inhibitor. Prior bevacizumab treatment is allowed.
Exclusion Criteria	Participants who meet any of the following criteria will not be eligible for participation in this study: 1. Chemotherapy, biological therapy, immunotherapy, targeted therapy (including small molecule inhibitor of tyrosine kinase), and other antitumor therapy within 4 weeks or 5 half-lives (whichever is shorter) prior to the first administration; radical radiotherapy, major surgery within 4 weeks prior to the first administration; mitomycin and nitrosoureas treatment within 6 weeks prior to the first administration; oral drugs such as capecitabine, or palliative radiotherapy within 2 weeks prior to initial administration. 2. Received systemic immunostimulatory therapy (such as IFN-α, IL-2) within 4 weeks prior to the first dose or is still within 5 half-lives of the treatment (whichever is longer). 3. Received immunosuppressive drugs (e.g., corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, or anti-TNF-α agents) within 2 weeks before the first dose, except for: low-dose systemic glucocorticoids (≤10 mg/day prednisone equivalent); glucocorticoids administered for chronic obstructive pulmonary disease (COPD), antiemetic therapy, or infusion reactions; and topical, inhaled, or locally injected corticosteroids. 4. Participants with history of severe heart disease, such as symptomatic congestive heart failure Grade ≥2 (CTCAE 6.0), New York Heart Association (NYHA) Grade ≥2 heart failure at any time, history of myocardial infarction or unstable angina pectoris within 6 months before enrollment. 5. Participants with prolonged QT interval (QTcF >470 msec), complete left bundle branch block, Grade 3 atrioventricular block, or a history of additional risk factors for Torsades de Pointes (TdP; e.g., heart failure as defined in Exclusion Criterion 4, chronic or recurrent hypokalemia that requires medical intervention, congenital long QT syndrome, family history of long QT syndrome) or any current concomitant medication known to prolong the QT/QTc interval or cause TdP. 6. Among subjects who have been treated with prior immunotherapy, subjects with prior ≥ Grade 3 irAEs that lead to permanent discontinuation and/or any history of life-threatening irAEs including but not limited to pneumonitis, myocarditis, neurologic autoimmune toxicity; and/or subjects with prior irAEs requiring prolonged immunosuppressive therapy (>12 weeks). Note: Subjects who have previously experienced any of the following conditions are permitted to participate: • Experienced prior Grade ≤2 irAEs that have resolved to Grade ≤1 or baseline

- Are off systemic immunosuppression or on physiologic/replacement doses (≤10 mg prednisone equivalent)

7. Grade ≥ 3 toxicity related to anti-angiogenic therapy (except for fever and other toxicities that the investigator believes do not pose a safety risk to trial participants) when receiving anti-angiogenic therapy in the past.
8. Other malignant tumors were diagnosed within 5 years prior to the first administration with the following exceptions: basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or carcinoma in situ after radical resection.
9. For the dose escalation portion of the study only, participants with a primary diagnosis of lung cancer (including NSCLC, small cell lung cancer, and other thoracic pulmonary malignancies) are excluded.
10. Participants with a thromboembolic event (e.g., deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 6 months before Screening.
11. Participants with active or recent clinically significant bleeding are excluded:
    - Any history of intracranial or spinal hemorrhage (absolute contraindication).
    - Any Grade ≥2 hemorrhage within 12 months prior to enrollment (including GI, pulmonary, genitourinary, other).
    - Active bleeding of any type.
        - Unhealed hemorrhagic ulcers.
        - Vasculitis with active or recent bleeding.

    Note: All other bleeding events: Must be >12 months prior with documented imaging confirmation of resolution (for significant events) and investigator discretion.
12. Subjects with clinically significant platelet abnormalities or coagulopathy; adequate platelet counts and coagulation parameters must be confirmed, and any reversible coagulopathy corrected prior to dosing.
13. Subjects requiring full-dose anticoagulation or high-intensity antiplatelet therapy on high dose nonsteroidal anti-inflammatory drugs (NSAIDs) are excluded.
14. Diabetic patients with poor glycemic control, including but not limited to:
    a) 2 fasting blood glucose >10mmol/L,

    OR

    b) Concomitant diabetic gangrene.
15. Participants with poorly controlled hypertension by 2 kinds of antihypertensive drugs (systolic blood pressure>150 mmHg or diastolic blood pressure>100 mmHg).
16. Participants with stroke or transient ischemic attack (TIA) within 6 months before Screening.
17. Active autoimmune diseases and inflammatory diseases, such as systemic lupus erythematosus, psoriasis requiring systemic treatment, rheumatoid arthritis, inflammatory bowel disease and Hashimoto's thyroiditis, etc. Participants with skin diseases that do not require systemic treatment (such as vitiligo, psoriasis), well-controlled type 1 diabetes, or hypothyroidism are permitted. For autoimmune conditions that are active but stable and low-grade on systemic therapy, discussion with the medical monitor is required prior to Screening.

    Note: Active autoimmune or inflammatory disease is defined as disease within 6 months with clinically significant flare, new/progressive clinical signs, or objective inflammation requiring intervention or corticosteroid dose >10 mg prednisone equivalent daily. Stable disease on unchanged maintenance immunosuppression for ≥6 months, positive serology without clinical activity, or

	well-controlled endocrinopathies on hormone replacement alone do not constitute active disease. 18. Participants with advanced/clinically significant lung diseases, such as poorly controlled COPD and asthma, restrictive lung disease, pulmonary hypertension, etc. 19. Participants who have a history of noninfectious interstitial lung disease (ILD)/pneumonitis that required treatment with steroids, have current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening. 20. Concurrent pulmonary disease resulting in severe impaired respiratory function, including but not limited to the following: a) Any underlying pulmonary disease (e.g., pulmonary embolism, severe asthma, severe COPD within 3 months prior to information). b) Restrictive lung disease. c) Previous unilateral total lung resection. 21. Participants with pulmonary hemorrhage risk: evidence on baseline chest imaging of pulmonary hemorrhage risk, including cavitary primary lung lesions, central tumors with major vessel encasement/invasion, or other imaging findings judged by the investigator to confer unacceptable risk of hemorrhage. 22. Participants with chest-pelvic effusion requiring drainage and/or symptomatic pleural-pelvic effusion, or pericardial effusion within 4 weeks prior to Screening. 23. Participants with primary tumors in the central nervous system (CNS), active or untreated CNS metastases or carcinomatous meningitis should be excluded. Participants with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks and have no evidence of new or enlarging brain metastases and no requirements for corticosteroids 14 days prior to Screening. Clinically stable CNS metastasis is defined as: a) Seizure-free state lasting > 12 weeks with or without antiepileptic drugs. b) Stable imaging as evidenced by consecutive MRIs at least 4 weeks apart. 24. Participant with active or untreated hemorrhagic CNS lesions. 25. Participants with pre-existing Grade ≥2 peripheral neuropathy. 26. Participants with a history of anaphylaxis or severe hypersensitivity reactions to: a) recombinant humanized antibodies or human–mouse chimeric antibodies. b) any component of SI-B037. 27. Previous organ transplantation or allogeneic hematopoietic stem cell transplantation. 28. Subjects with recent surgery, biopsy, or invasive procedures without adequate wound healing prior to study enrollment. 29. Participants with known or suspected human immunodeficiency virus (HIV) infection (HIV antibody positive). Exceptions: Participants are allowed to participate if **all** the following criteria are met: • undetectable HIV RNA and CD4 count ≥350 cells/μL at Screening. • no acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 12 months prior to Screening. **AND** • on stable antiretroviral therapy (ART) for at least 4 weeks prior to enrollment, with projected continuation of ART as clinically indicated while on the study. 30. Participants with known active hepatitis B virus (HBV) infection (positive hepatitis B surface antigen [HBsAg] test).

	Exceptions: Participants with a chronic inactive HBV infection are eligible if all the following criteria are met: • HBV DNA viral load <500 IU/mL. • normal AST and ALT, or if liver metastasis is present, AST and ALT <3 × ULN that are not attributed to HBV infection. **AND** • on antiviral treatment as clinically indicated. 31. Participants with known active hepatitis C virus (HCV) infection (HCV antibody positive and HCV-RNA > the lower limit of detection). Exception: Participants with a positive anti-HCV antibody are eligible only if quantitative polymerase chain reaction (qPCR) is negative for HCV-RNA. 32. Participants with active or latent tuberculosis. 33. Participants with active infections requiring IV antibiotic, antiviral, or antifungal treatment, such as severe pneumonia, bacteremia, sepsis, etc., within 1 week prior to first dose of study treatment. Participants on stable oral antimicrobials with no clinical or laboratory evidence of active infection are eligible. 34. Participated in another clinical trial within 4 weeks prior to first dose of study treatment. 35. Participants who are pregnant, breastfeeding, or planning to become pregnant during the study. 36. History of fistula, gastrointestinal perforation, or abdominal abscess within 6 months prior to the first dose. 37. Participant with moderate or major hemoptysis history. 38. Participant has tumors invading large blood vessels. Imaging examination shows that the tumor has: • tumor has invaded or wrapped around the large blood vessels of the chest such as pulmonary artery, aorta, pulmonary vein, etc. (physician's discretion). • tumor has invaded or wrapped pericardium and heart (physician's discretion). 39. Other conditions that the investigator or sponsor believes are not suitable for participating in this clinical trial.
Study Procedures	Study Procedures are detailed in Section 6 and Section 8 of the protocol. Dose, route, and frequency of administration are described below: **Dosing Regimen** SI-B037 will be administered IV on Day 1 in a 3-week cycle. The first IV infusion duration will be 120 minutes ±10 minutes. If no infusions reactions occur during the first dose, subsequent infusions can be completed in 60 to 120 minutes. If the participant has experienced an infusion reaction, which was mild (Grade 1) or manageable (Grade 2), the participant should receive prophylactic premedication at least 30 minutes before subsequent administration. The initial IV duration should be 120 minutes ±10 minutes. Reducing the infusion time to 60 to 120 minutes may be attempted once, if the subject has not experienced an IRR for 2 consecutive infusions. Dose reductions will be conducted according to Table S2. **Table S2 Dose Reductions** **SI-B037** **First dose reduction** | **Second dose reduction** Reduce by 20% of initial dose | Reduce by 40% of initial dose Note: A maximum of 2 dose reductions will be allowed

	Dose reduction will be performed according to CTCAE v6.0. A list of toxicities and the required action or rule is provided in Table 9 of the protocol. Participant discontinuation and withdrawal are described in Section 7.2 of the protocol. In addition, treatment will stop for an individual participation if the subject experiences: • Disease progression by response evaluation criteria in solid tumors (RECIST V1.1) (treatment beyond radiographic progression may be allowed if there is evidence of clinical benefit with continued therapy based on investigators judgment after discussing with the Sponsor). • Toxicity requiring discontinuation of investigational product as described in Table 9 of the protocol. The sponsor may decide to stop treatment for an individual participant on a case-by-case basis. The reason for participant discontinuation or withdrawal from the study and the date of this decision must be recorded on the eCRF. If the participant withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. If a participant discontinues treatment only, further evaluations and survival follow-up will be conducted. **Study Stopping Rules** The sponsor has the right to terminate this study or a study site from participating at any time. Reasons for terminating the study at a specific study site may include, but are not limited to: • Participant enrollment is unsatisfactory. • Data recording is inaccurate or incomplete. • Investigator does not adhere to the protocol or applicable regulatory requirements in conducting the study. Enrollment in the study will stop/pause to assess subject safety if any of the following occur: • The safety committee recommends termination for safety reasons. • The incidence or severity of AEs in this or other SI-B037 studies indicate a potential health hazard to subjects. • Death (other than disease progression) that is likely related to SI-B037. • All participants enrolled in the study have withdrawn from treatment, completed participation in the study or are lost to follow up.
Concomitant Medication	Enrolled participants will inform the study investigator about all prior and concomitant medications administered from the Screening visit to study termination (including the date and time of administration). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and supplements.
Prohibited Medication	The combined use of antitumor therapy (including chemotherapy, biological therapy, immunotherapy, radical radiotherapy, targeted therapy, herbal or holistic medicines with antitumor indications, retinoid therapy, nitrosourea therapy, mitomycin C, small molecule tyrosine kinase inhibitors [TKIs]), etc.), anticoagulants, antiplatelet therapies, live attenuated vaccines, high dose nonsteroidal anti-inflammatory drugs (NSAIDS), systemic immunosuppressants, drugs that may interact with SI-B037 or prolong the QT/QTc interval (Section 6.9) and other investigational drugs as described in the exclusion criteria (Section 5.2) is prohibited during the study period.
Statistical Methods	The BOIN design will be applied for guiding dose escalation/de-escalation strategies across the populations. During the dose escalation phase, 3 to 6 DLT-evaluable participants for each

	dose level (group of participants treated at a dose level to inform the next dose escalation/de-escalation decision) will be enrolled. **Efficacy Analysis** Efficacy variables will include ORR, DCR, DOR, TTR, PFS, and OS, using RECIST Version 1.1. The efficacy variables will be listed and summarized. For ORR and DCR, point estimates and two-sided 95% exact binomial confidence intervals will be provided. Time-to-event variables, including DOR, TTR, PFS, and OS, will be summarized descriptively using the Kaplan-Meier method. Censoring rules for time-to-event endpoints will be specified in the statistical analysis plan (SAP). **Safety Analysis** The safety profile will be based on AEs, serious adverse events (SAEs), death, clinical laboratory measurements, vital sign measurements, ECG recordings, and physical examination findings. AEs will be graded according to CTCAE v6.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. The tolerability will be assessed based on the incidence and severity of AEs. Key safety findings will be discussed in relation to the overall clinical context and aligned with the study objectives. **Pharmacokinetic Analysis** Pharmacokinetic analyses will be performed on the PK analysis set. Serum concentration-time data for SI-B037 will be listed, plotted, and summarized using descriptive statistics. PK parameters will be listed and summarized using descriptive statistics. **Exploratory Analysis** Exploratory analysis for biomarkers will be listed and summarized using descriptive statistics pending data availability. **Sample Size Determination** In the dose escalation phase, the sample size is approximately 18 DLT-evaluable participants. In the dose finding phase, up to 20 participants will be enrolled for each selected dose level. The dose expansion sample size has been determined by practical consideration, and no formal statistical assessments are planned in the study. In the dose expansion phase, participants will be randomized into 1 of 2 dose cohorts, with a maximum of 160 participants per dose level.

1.1.2. Primary and Secondary Objectives and Endpoints

Objectives and endpoints are described in Table S3.

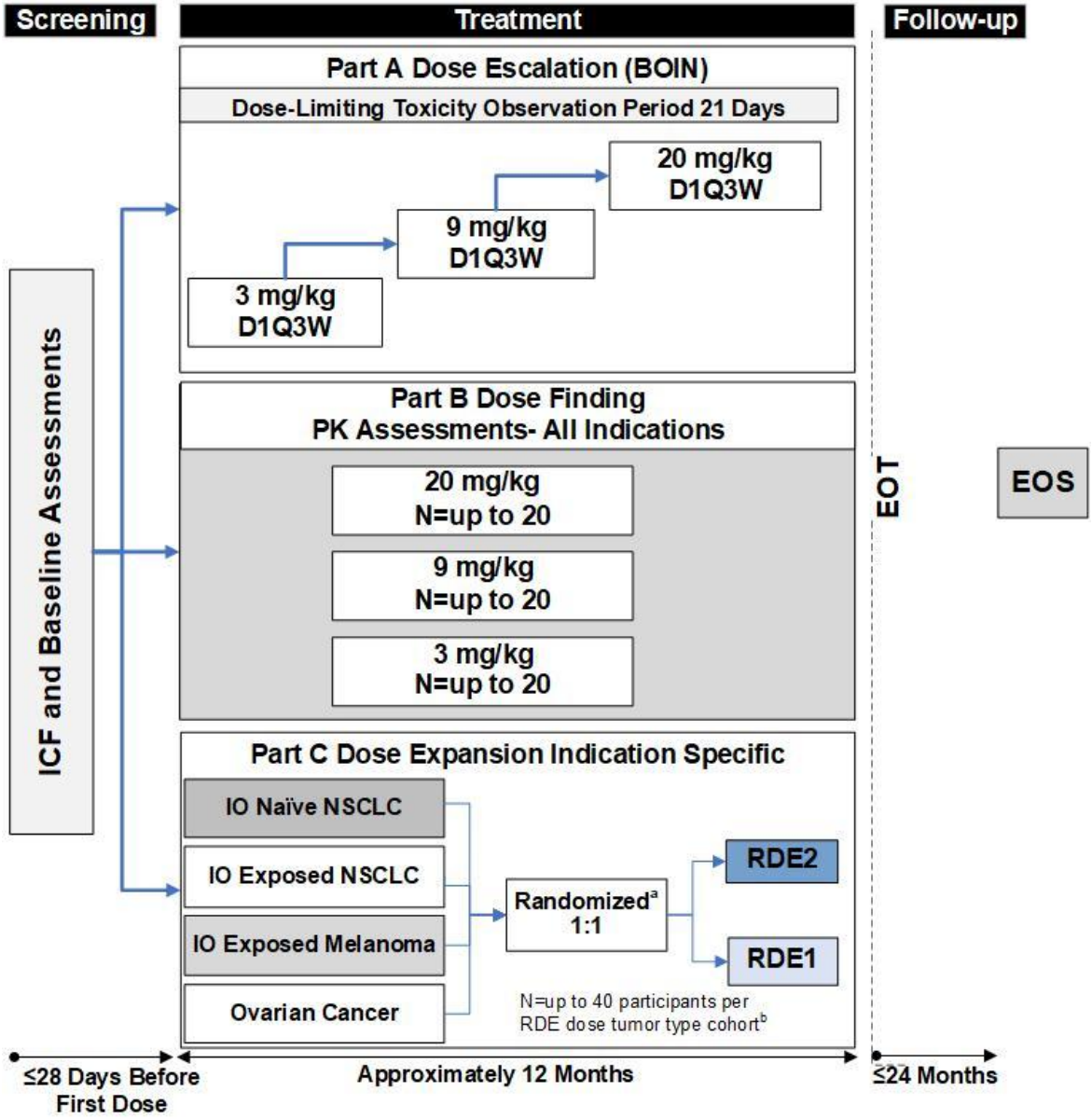
Table S3 SI-B037-ST-101 Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the safety and tolerability of SI-B037 in participants with solid tumors who have received at least one prior line of therapy for advanced disease	• Serious adverse events (SAEs), adverse events of special interest (AESI), TEAEs, death, TEAEs leading to discontinuation, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters (including the change-from-baseline ECG parameters: HR; PR, QTcF, and QRS intervals [ΔHR, ΔPR, ΔQTcF, and ΔQRS])
• To determine RDEs, the MSED if reached or MAD, MTD of SI-B037	• DLT

Secondary	
• To evaluate preliminary efficacy	• Objective Response Rate (ORR), Disease Control Rate (DCR), Progression-free survival (PFS), Overall survival (OS)
• To evaluate the pharmacokinetic characteristics of SI-B037	• Pharmacokinetic (PK) parameters: Cmax, T_{max}, $T_{1/2}$, AUC_{0-t}, CL, and $C_{trough,}$ etc.
Exploratory	
• To evaluate the immunogenicity of SI-B037	• Immunogenicity: incidence of anti-drug antibodies (ADAs) to SI-B037
• To identify biomarkers that correlate with SI-B037 response or toxicity	• To determine biomarkers obtained before and/or after treatment and/or during disease progression in archived and/or fresh tumor tissue and blood samples (e.g., PD-1, VEGF-A and other soluble proteins)

Abbreviations: ADA=anti-drug antibody; AUC_{08}=area under the serum concentration-time curve from time 0 to 8 hours; AUC_{last}=area under the serum concentration-time curve up to the last quantifiable time; C1D1=Cycle 1 Day 1; CL=clearance; C_{max}=maximum (peak) observed concentration in serum; DCR=disease control rate; DLT=dose-limiting toxicity; DoR=duration of response; PS=Eastern Cooperative Oncology Group performance status; ECG=electrocardiogram; HR=heart rate; IHC=immunohistochemistry; K_{el}=terminal elimination rate constant; MAD=maximum administered dose; mRNA= messenger RNA; MTD=maximum tolerated dose; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; QTcF=QT interval corrected (Fridericia formula); RDE=recommended dose for expansion; RECIST= Response Evaluation Criteria In Solid Tumors; SAE=serious adverse event; TAB=total antibody; TEAE=treatment-emergent adverse event; $t_{1/2}$=elimination half-life; T_{max}=time of maximum observed concentration; TTR=time to response; V_{ss}=apparent volume of distribution at steady-state after multiple doses; V_z=volume of distribution after a single dose.

1.2. Trial Schema



Abbreviations: BOIN= Bayesian Optimal Interval; D1Q3W=day 1 every 3 weeks; EOS=end of study; EOT=end of treatment; ICF=informed consent form; IO=Immuno-oncology; OC=ovarian cancer; NSCLC=non-small cell lung cancer; PK=pharmacokinetics; RDE= recommended dose for expansion

a. Participants for each tumor cohort will be randomized to receive either RDE1 or RDE2.
b. Up to 80 participants per tumor type (up to 40 per RDE dose) will be randomized to receive SI-B037 at either RDE1 or RDE2.

*Note: RDE1 is the lower dose that will be chosen for expansion, also known as Dose -1. RDE2 will be the RP2D and the higher dose chosen for expansion.

1.3. Schedule of Activities (SOA)

Table 1 Schedule of Activities

			Cycle 1					Cycle2			Cycle 3 and Subsequent Cycles [bb]			EOT [w]	Safety Visit [x]	Follow-up [y]
Activities Study Period (Day)	**Screening Period**		**1**	**2**	**3**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**			
Assessment Window (days)	**−28**	**−7**	**NA**			**±2**		**+3**	**±2**		**-1/±3**	**±2**		**NA**	**40+7**	**NA**
Adverse Events [a, bb]	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Demographics [b]	X															
Echocardiography/MUGA	X															
ECOG assessment	X		X	X	X	X	X	X	X	X	X			X	X	
Enrollment number	X															
Height, weight [c]	X	X	X					X			X			X	X	
Informed Consent	X															
Inclusion/Exclusion criteria	X	X														
Medical History [d]	X															
Physical examination [e]	X	X	X					X			X			X	X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Prior anticancer treatments [d]	X															
Screening eligibility form		X														
Triplicate ECG [f]	X		X	X	X	X	X	X			X			X		
Tumor tissue Sample [g]	X															
Vital signs [h]	X	X	X			X		X	X		X			X	X	
Laboratory Assessments																
Angiogenic/Biomarker detection [z]			X	X		X	X	X			X					
Cardiac markers [i]	X		X					X			X					
Chemistry Panel [j]		X	X			X	X	X	X	X	X			X	X	
Coagulation function [k]		X	X			X		X	X		X			X		

Activities Study Period (Day)	Screening Period		Cycle 1					Cycle2			Cycle 3 and Subsequent Cycles [bb]			EOT [w]	Safety Visit [x]	Follow-up [y]
			1	2	3	8	15	1	8	15	1	8	15			
Assessment Window (days)	**−28**	**−7**	**NA**			**±2**		**+3**	**±2**		**-1/±3**	**±2**		**NA**	**40+7**	**NA**
FSH [l]	X															
Hematology [m]		X	X			X	X	X	X	X	X			X		
Hepatitis B & C [n]	X															
HIV testing [n]	X															
Immunogenicity [o]			X			X	X	X			X			X		
Pregnancy test [p]		X						X			X			X		
PK blood collection [q]			X (Table 2 and Table 3)													
Thyroid function [aa]		X	X					X			X			X		
Urinalysis[r]		X	X					X			X			X	X	
Efficacy Assessment																
Tumor evaluation (includes brain imaging at Baseline) [s,t]	X		X (assessed every 6 weeks ± 7 days in the first year of medication; In the second year of medication, every 12 weeks ±7 days of assessment)											X	X	X
Whole-body bone nuclide scan (if necessary) [u]	X		*Optional per PI*											X	X	X
Trial Treatment Administration [v]			X					X			X					

Abbreviations: AE=adverse events; anti-HBc=Hepatitis B core antibody; anti-HBe=Hepatitis B e antibody; APTT=activated partial thromboplastin time; BNP=B-type natriuretic peptide; CK-MB=creatine kinase isoenzyme MB; ConMeds=concomitant medications; CT=computerized tomography; cTn=cardiac troponin; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; fib=fibrinogen; FFPE=formalin-fixed, paraffin-embedded; HBsAg=Hepatitis B surface antigen; HBeAG=Hepatitis B e antigen; HBV=Hepatitis B virus; HCV=Hepatitis C virus; ICF=informed consent form; INR=international normalized ratio; Mb=myoglobin; MRI=magnetic resonance imaging; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic; PT=prothrombin time; TT=thrombin time; ULN=upper limit of normal.

SOA Footnotes

a. After the Safety Follow-up Visit, only SAEs that are related to the study drug will be followed and reported to sponsor.

b. Demographic information includes date of birth or age, sex, race, and ethnicity.

c. Height is measured only during the screening period. The subject's baseline weight (Cycle 1 Day 1 with a 1-day window) will be used to calculate the dose of the drug for all cycles unless there is a documented ±10% change-from-baseline weight. If there is a documented ±10% change-from-baseline weight, the subject's dose must be recalculated, per Section 8.4.1.1: for participants with a body weight ≥100 kg, the maximum administered dose will be capped at the dose calculated for a body weight of 100 kg to limit excessive exposure in participants with very high body weight.'

d. History includes past and present medical history. Record the medical history, surgical history, etc. within 5 years before signing the ICF (excluding the history of the target tumor), and record the previous medication within 4 weeks before signing the ICF (focusing on the antitumor treatment drugs); The present medical history records the date of first diagnosis of the target tumor, the overall stage of the tumor, the overall stage of the tumor during the screening period, the history of tumor treatment, etc., and the treatment drug records the treatment plan 8 weeks before signing the ICF, including the history of surgery, chemotherapy, radiotherapy, anticancer medicine and molecular targeted therapy. Keep a history of smoking and drinking.

e. A complete physical examination is performed at baseline and at termination of treatment according to Section 8.4.1. During other visits, a targeted/symptom focused physical examination (as judged by the investigator) will be performed.

f. Record all ECG conditions and corresponding values of the ECG, including but not limited to heart rate, P-R interval, QRS interval, QT interval, QTc interval, etc.

   1. Cycle 1 Day 1: All participants should undergo routine ECG monitoring (triplicate reading, 1 to 3 minutes between readings, all 3 completed within 5 minutes) starting within 30 minutes before the first dose, within 15 minutes after the end of the infusion, then 2 hours ±30 minutes and 4 hours±30 minutes after the end of the infusion via 12-lead ECG.

   2. Subsequent Cycles: ECG performed only within 30 minutes before administration and within 15 minutes after the end of the infusion. If clinically indicated, the investigator may add a 12-lead ECG reading. Repeat ECG as necessary if QTc >500 ms or 60 ms over baseline. ECG monitoring should follow the PK blood collection schedule provided in Table 2 and Table 3.

   NOTE: For timepoints where both ECGs and PK/biomarker samples are collected, ECGs should be done prior to the blood draw. On days other than Day 1 of any cycle, the ECGs should occur within 30 minutes prior to the PK blood draw (Table 2 and Table 3)if applicable.

g. All subjects during the screening period are required to provide tumor tissue samples (Section 8.1) to a central laboratory for exploratory analysis. If no archival tissue is available and a fresh tissue biopsy is clinically contraindicated, please consult the sponsor.

h. Vital signs include pulse, blood pressure, breathing, and temperature. If clinically indicated, it is up to the investigator to determine whether to increase vital signs surveillance.

i. Cardiac markers tests include Mb, BNP, CK-MB, and cTn, of which Mb and CK-MB tests are determined according to the actual situation of the center and are not required.

j. To be assessed locally. Blood chemistry includes alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, alkaline phosphatase, total protein, albumin, urea, creatinine, fasting blood glucose, total cholesterol, triglycerides, lactate dehydrogenase, and electrolytes including magnesium and phosphate. The testing window before the first infusion is within 3 days prior to Day 1 of infusion, and the window for subsequent infusions is within 2 days prior to Day 1 of infusion. Screening and pre-C1D1 safety labs are separate panels. Study drug can only be administered after the test results are reviewed.

k. Coagulation function: PT, APTT, TT, FIB, and INR.

l. Postmenopausal status in female subjects <55 years old must be confirmed by serum follicle stimulating hormone (FSH) test at Screening, unless they have undergone hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.

m. To be assessed locally. Blood tests include reticulocytes, hemoglobin, red blood cell count, white blood cell count, neutrophil count, lymphocyte count, eosinophil count, basophil count, monocyte count, and platelet count. The testing window before the first infusion is within 3 days prior to Day 1 of infusion, and the window for subsequent infusions is within 2 days prior to Day 1 of infusion. Screening and pre-C1D1 safety labs are separate panels. Study drug can only be administered after the test results are reviewed.

n. For subjects with known HIV or Hepatitis C status: HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, Hepatitis C antibody and HIV detection, HBV DNA quantitative PCR test for HBsAg-positive subjects, and HCV-RNA quantitative detection for HCV antibody positive subjects.

o. Samples will be taken for ADAs as described in Table 2 and Table 3.

p. A serum pregnancy test will be performed (if applicable) during the screening period to exclude pregnancy no more than 3 days before the subject receives their first treatment. Pregnancy status will then be assessed (urine or serum) every cycle starting on Cycle 2. If pregnancy is suspected during a visit, an additional serum/urine pregnancy test should be performed and the sponsor notified. An additional pregnancy test should be performed at EOT.

q. For details of pharmacokinetic blood collection points, see Table 2 and Table 3

r. Urine testing for proteinuria may be performed using dipstick urinalysis; positive findings (≥1+) should be confirmed and quantified per institutional standards.

s. Enhanced CT or enhanced MRI (CT layer thickness is less than 5mm) is the preferred choice for tumor assessment. For subjects allergic to CT contrast, plain CT scan or enhanced MRI can be performed; and for special lesions (such as skin lesions), only clinical examination is acceptable (relevant color photos shall be archived). Imaging examination at baseline shall inspect the neck (if clinically indicated), chest, abdomen, and pelvis and enhanced MRI of the brain. If the subject has received an imaging examination within 28 days prior to the first dose with satisfactory results, repeated examination may not be required. All subjects shall undergo brain imaging examinations at baseline, preferably enhanced brain MRI. The same imaging technique shall be applied throughout the study. If disease progression is suspected during the study, additional imaging examination can be performed at any time. Since the first dose, imaging examinations shall be conducted once every 6 weeks ±7 days in the first 52 weeks of treatment; then once every 12 weeks ±7 days afterwards; until start of new antitumor drug therapy, or disease progression, death, loss to follow-up, withdrawal of informed consent by the subject, or discontinuation of the study by the sponsor, whichever occurs first.

t. For subjects who discontinue treatment without disease progression, tumor imaging evaluation will be performed once every 6 weeks ±3 days in the 52 weeks after safety visit; and once every 12 weeks ±3 days until start of new antitumor drug therapy, disease progression, death, loss to follow-up, withdrawal of informed consent by the subject, or discontinuation of the study by the sponsor, whichever occurs first.

u. During the study, the investigator determines if bone scintigraphy is required based on the subject's status and clinical decision-making needs.

v. SI-B037 is administered on Day 1 in a 3-week cycle. For Cycle 2, the dosing window is +3 days with a minimum dosing interval of 21 days. Starting at Cycle 3, the dosing interval is -1/+3 days with a minimum dosing interval of 20 days. If a dose is delayed, subsequent visits will be based on the actual D1 of that cycle. The rules to delay, reduce, or discontinue the dose are presented in Section 6.6.

w. The end of treatment (EOT) visit occurs within 7 days of the decision to leave the trial. If the subject terminates treatment for reasons other than disease progression, they will undergo imaging examination for efficacy assessment. Subjects with test results obtained within 7 days prior to the discontinuation of treatment do not need to be retested. TEAEs will be followed until 30 days after discontinuation; AESI or Treatment-related serious adverse events (TRSAE) will be followed until 60 days after discontinuation. .

x. Safety follow-up will be 40 (+7) days after the last IP administration or before starting new anticancer treatment, whichever comes first. TEAEs that are ongoing at the safety follow-up, will be followed until resolve or study discontinuation/patient withdraw/loss of FU. SAEs will be followed until the conditions resolve or return to baseline, or until start of new systemic non-protocol anticancer therapy (NPACT). See details in Section 8.5 Only SAEs that are assessed as related to study drug by investigator will be collected after safety follow-up.

y. Overall survival (OS) will be assessed every 12 weeks (± 14 days) after the safety visit, which occurs 40 (+7) days after the date of the decision to discontinue study treatment. Subjects will be followed until death or sponsor decision to no longer collect these data. Receipt of new systemic NPACT will also be collected during follow-up contacts. If a subject withdraws consent for noninterventional study assessments, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations.

z. During the dose escalation phase (Part A) and dose finding phase (Part B), blood will be collected to assess VEGF-A and PD-1 levels as displayed in Table 2 and Section 8.1; additional blood collection time points may be prospectively adjusted based on preliminary biomarker data. Blood samples will be collected at 2 predefined time points: 4 hours prior to dosing and 2 hours post-dose. VEGF-A and PD-1 levels will be centrally tested (see also Section 8.1).

aa. See Appendix 2

bb. For Cycle 4 only, reference PK Table 2 and PK Table 3 for Day 15 visit.

Table 2 Pharmacokinetic and Immunogenicity Blood and ECG Collection Schedule (Part A-Dose Escalation and Part B-Dose Finding)

Study Day of Sample Collection	SI-B037 Event	Window Relative to SI-B037 Event	Blood Sample for PK [a, b]	Blood Sample for ADA [b,c]	Triplicate ECG[d]	VEGF-A and PD-1
Cycle 1 Day 1	Pre-infusion	Within 4 hours before	X	X	X	X
Cycle 1 Day 1	End of infusion	+15 minutes after	X		X	
Cycle 1 Day 1	End of infusion	2 hours ±30 minutes after	X		X	X
Cycle 1 Day 1	End of infusion	4 hours ±30 minutes after	X		X	
Cycle 1 Day 2	End of infusion	24 hours ±1 hour after	X		X	X
Cycle 1 Day 3	End of infusion	48 hours ±2 hours after	X		X	
Cycle 1 Day 8	End of infusion	168 hours ±4 hours after	X	X	X	X
Cycle 1 Day 15	End of infusion	336 hours ±4 hours after	X	X	X	X
Cycle 2 & 3 Day 1	Pre-infusion	Within 4 hours before	X	X	X	X
Cycle 2 & 3 Day 1	End of infusion	+15 minutes after	X		X	
Cycle 2 & 3 Day 1	End of infusion	2 hours ±30 minutes after	X		X	X
Cycle 4 Day 1	Pre-infusion	Within 4 hours before	X	X	X	X
Cycle 4 Day 1	End of infusion	+15 minutes after	X		X	
Cycle 4 Day 1	End of infusion	2 hours ±30 minutes after	X		X	X
Cycle 4 Day 1	End of infusion	4 hours ±30 minutes after	X		X	
Cycle 4 Day 2	End of infusion	24 hours ±1 hour after	X		X	
Cycle 4 Day 3	End of infusion	48 hours ±2 hours after	X		X	
Cycle 4 Day 8	End of infusion	168 hours ±4 hours after	X		X	
Cycle 4 Day 15	End of infusion	336 hours ±4 hours after	X		X	X
Cycle 5 Day 1	Pre-infusion	Within 4 hours before	X	X	X	X

Cycle 5 Day 1	End of infusion	+15 minutes after	X		X	
Cycle 5 Day 1	End of infusion	2 hours ±30 minutes after	X		X	X
Cycle7,9,11,13,15,17, 19,21,23,25,27,29,31,33 Day 1	Pre-infusion	Within 4 hours before	X	X	X	X
Cycle 7,9,11,13,15,17,19,21,23,25,27,29,31,33 Day 1	End of infusion	+15 minutes after	X		X	
EOT			X	X	X	

a. For dose escalation and dose finding parts: Collect pre- and post- infusion on Day 1 every other cycle [eg, Cycle 7 Day 1 (C7D1), Cycle 9 Day 1 (C9D1), Cycle 11 Day 1 (C11D1), etc.] starting from Cycle 7.
b. Always collect a pre-infusion PK sample simultaneously with all immunogenicity (ADA) samples in Cycles 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and EOT, regardless of PK collection schedule in footnote ‘a’. Collect C1D8 and C1D15 PK sample with ADA sample.
c. During dose escalation, dose finding and dose expansion, ADA sample collection will remain on the same schedule.
d. For the time points where both ECGs and PK samples are collected, ECGs should occur within 30 minutes prior to the PK blood draw or infusion.

Note: the end of infusion time point is after a post infusion saline flush

Table 3 Pharmacokinetic and Immunogenicity Blood and ECG Collection Schedule (Part C-Dose Expansion)

Study Day of Sample Collection	SI-B037 Event	Window Relative to SI-B037 Event	Blood Sample for PK [a, b]	Blood Sample for ADA [b,c]	Triplicate ECG[d]
Cycle 1 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 1 Day 1	End of infusion	+15 minutes after	X		X
Cycle 1 Day 1	End of infusion	2 hours ±30 minutes after	X		X
Cycle 1 Day 1	End of infusion	4 hours ±30 minutes after	X		X
Cycle 1 Day 8	End of infusion	168 hours ±4 hours after	X	X	X
Cycle 1 Day 15	End of infusion	336 hours ±4 hours after	X	X	X
Cycle 2 & 3 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 2 & 3 Day 1	End of infusion	+15 minutes after	X		X
Cycle 2 & 3 Day 1	End of infusion	2 hours ±30 minutes after	X		X
Cycle 4 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 4 Day 1	End of infusion	+15 minutes after	X		X
Cycle 4 Day 1	End of infusion	2 hours ±30 minutes after	X		X
Cycle 4 Day 1	End of infusion	4 hours ±30 minutes after	X		X
Cycle 4 Day 15	End of infusion	336 hours ±4 hours after	X		X
Cycle 5 & 7 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 5 & 7 Day 1	End of infusion	+15 minutes after	X		X
Cycle 9 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 13 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 17 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 25 Day 1	Pre-infusion	Within 4 hours before	X	X	X
Cycle 33 Day 1	Pre-infusion	Within 4 hours before	X	X	X
EOT			X	X	X

a. For dose expansion: Sparse PK sampling is required as shown in the table above. No additional PK samples are required after Cycle 7 except pre-infusion samples in Cycle 9,13, 17, 25, and 33.
b. Always collect a pre-infusion PK sample simultaneously with all immunogenicity (ADA) samples in Cycles 1, 2, 3, 4, 5,7, 9, 13, 17, 25, 33 and EOT, regardless of PK collection schedule in footnote 'a'. Collect C1D8 and C1D15 PK sample with ADA sample.
c. During dose escalation, dose finding and dose expansion, ADA sample collection will remain on the same schedule.
d. For the time points where both ECGs and PK samples are collected, ECGs should occur within 30 minutes prior to the PK blood draw or infusion.

Note: the end of infusion time point is after a post infusion saline flush

2. INTRODUCTION

SI-B037 is a tetravalent, bispecific antibody that binds to and inhibits the activity of proven anticancer targets VEGF-A and PD-1. SI-B037 is composed of a bevacizumab IgG1 backbone (targeting VEGF-A) with a C-terminal scFv binding PD-1, linked to an engineered IgG1 Fc with a glycine + serine (GS) linker. This construct enables simultaneous blockade of tumor angiogenesis and immune checkpoint inhibition within a single molecule.

The ability of SI-B037 to bind PD-1 and VEGF-A was demonstrated in ELISA, cell-based, and bio-layer interferometry assays. These assays indicated that SI-B037 binds both targets with high affinity and potency comparable to the PD-1 antibodies nivolumab and pembrolizumab, the anti-VEGF-A antibody bevacizumab, and the PD-1 × VEGF-A bispecific antibody ivonescimab. Cell-based studies further demonstrated binding to PD-1-expressing cells in the presence and absence of VEGF-A, supporting independent engagement of both targets by SI-B037.

Consistent with the NAM-based development strategy agreed with FDA, SI-B037 was assessed for toxicity using human peripheral blood mononuclear cell (PBMC) cytokine release assays and human Liver-Chip, Kidney-Chip, and Lung-Chip microphysiological systems rather than repeat-dose animal studies. SI-B037 was evaluated alongside comparator molecules including pembrolizumab, bevacizumab, ivonescimab, and SI-159FS3. In human PBMC assays, cytokine responses induced by SI-B037 remained within the range observed for comparator antibodies and were substantially lower than responses induced by the positive controls SEB and TGN1412. In a confirmatory study using GMP clinical material, SI-B037 similarly did not behave as a cytokine-release outlier relative to comparator antibodies.

In the Liver-Chip model, SI-B037 produced low ALT levels and only a modest reduction in albumin secretion, indicating no evidence of hepatocellular injury. In the Kidney-Chip model, SI-B037 demonstrated a mild renal stress signal that was comparable to bevacizumab and consistent with the known effects of VEGF-A pathway inhibition, without loss of barrier integrity or evidence of overt renal toxicity. In the Lung-Chip model, SI-B037 did not increase SP-D, a marker of lung injury, and no structural disruption of the alveolar-capillary barrier was observed. Collectively, these studies did not identify any new, severe, or unexpected toxicity associated with SI-B037 relative to approved comparator antibodies or the related bispecific antibody ivonescimab.

Based on the totality of the nonclinical pharmacology and toxicology data, SI-B037 demonstrated specific binding to PD-1 and VEGF-A and a nonclinical safety profile that supports advancement into a carefully monitored first-in-human (FIH) clinical study.

2.1. Purpose of Trial

The purpose of this open-label study is to evaluate the safety, tolerability, pharmacokinetic (PK) characteristics, and preliminary efficacy of SI-B037 in participants with advanced or metastatic solid tumors that are refractory to standard therapies.

2.2. Mechanism of Action

The mechanism of action by which SI-B037 kills tumors are as follows: (1) SI-B037 blocks the PD-1 immune checkpoint signaling pathway, lifting immune suppression and activating cytotoxic T lymphocytes; (2) SI-B037 neutralizes VEGF-A, inhibiting new blood vessel formation necessary for sustained tumor growth and metastasis**.**

SI-B037 incorporates the VEGF-A-binding Fab domains derived from bevacizumab, which neutralizes VEGF-A by preventing its interaction with VEGFR-1 and VEGFR-2 (Ferrara et al. 2004). SI-B037 uses human IgG1 frameworks with an Fc region retaining FcRn binding for recycling and t½ extension, while effector functions (antibody-dependent cellular cytotoxicity [ADCC] /compliment-dependent cytotoxicity [CDC]) are minimized through Fc engineering (Zhong et al. 2025). As a result, SI-037 shares an anti-angiogenic mechanism with ivonescimab and is expected to demonstrate similar on-target class effects associated with VEGF-A inhibition, including hypertension, proteinuria, and delayed wound healing.

2.3. PD-1 as a Therapeutic Target

As a key regulator of immune homeostasis, programmed cell death protein 1 (PD-1) is an inhibitory immune checkpoint receptor expressed primarily on activated T cells, B cells, and other immune-cell populations. Engagement of PD-1 by its ligands, PD-L1 and PD-L2, downregulates the magnitude of immune responses and contributes to peripheral tolerance. Tumor cells and cells within the tumor microenvironment frequently exploit the PD-1 pathway to evade immune surveillance by promoting inhibitory signaling in tumor-reactive lymphocytes (Kythreotou et al. 2018). Therefore, PD-1 represents an established and clinically validated target for anticancer immunotherapy.

It is well-established that blockade of the PD-1/PD-L1 axis with anti-PD-1 or anti-PD-L1 agents restores T-cell receptor-mediated signaling pathways, including Ras-Raf-MEK-ERK and PI3K-AKT signaling, thereby reversing PD-1-mediated immune suppression (Patsoukis et al. 2012). As a result, PD-1 pathway inhibition can reinvigorate exhausted T cells and enhance antitumor immune activity (Yi et al. 2018).

PD-1-targeting antibodies, including nivolumab (Opdivo), pembrolizumab (Keytruda), and cemiplimab (Libtayo), have been approved by the FDA and EMA for the treatment of multiple malignancies (Bristol-Myers Squibb Company 2025; Merck & Co 2026; Regeneron Pharmaceuticals Inc 2025). SI-B037 contains an antibody that binds to PD-1 expressed on T cells and blocks its interaction with PD-L1. By preventing PD-1-mediated inhibitory signaling, SI-B037 is designed to restore T-cell effector function and enhance antitumor immune responses, a clinically validated therapeutic approach in the treatment of cancer.

2.3.1. VEGF-A as a Therapeutic Target

The vascular endothelial growth factor A (VEGF-A) pathway is one of the most important signaling pathways in the angiogenesis process, and many inhibitors have been developed to block the action of VEGF and its receptors (VEGFRs), with more than 10 approved drugs for various tumors being used in clinical practice (Ribatti 2025), making therapeutic interventions that inhibit the VEGF pathway a mainstay of cancer treatment.

VEGF-A exerts its biological effects primarily through binding and activation of vascular endothelial growth factor receptor 2 (VEGFR-2), the major signaling receptor responsible for endothelial cell proliferation, migration, survival, and vascular permeability. In cancer, overexpression of VEGF-A promotes the formation of abnormal tumor vasculature, facilitating tumor growth, progression, and metastasis (Marques, Brandão, and Burke 2024). Due to rapid proliferation and metabolic demands, tumor cells frequently experience hypoxia and nutrient deprivation within the tumor microenvironment (TME) (Kerbel 2008). Hypoxia induces the expression and secretion of VEGF-A and other pro-angiogenic mediators including basic fibroblast growth factor (bFGF) and matrix metalloproteinases (MMPs) (Ronca et al. 2017). Sustained overproduction of VEGF-A disrupts the balance between pro- and anti-angiogenic factors, resulting in persistent activation of angiogenic pathways and the development of structurally abnormal blood vessels (Sato 2003) (Jain 2003).

Tumor blood vessels induced by VEGF-A are frequently disorganized, poorly covered by pericytes, and highly permeable (Dvorak 2002). These abnormalities contribute to elevated vascular permeability and increased interstitial fluid pressure within tumors (Cooke et al. 2012), which may impair immune-cell infiltration and contribute to an immunosuppressive microenvironment (Simsek and Klotzsch 2022). Accordingly, inhibition of VEGF-A has the potential not only to reduce tumor angiogenesis but also to improve vascular normalization and enhance antitumor immune responses (Kang, Chen-Fu, and Guo-Wu 2021; Altaf, Mohammad, and Salman 2021).
Bevacizumab, a monoclonal antibody that binds to and blocks the function of VEGF-A, was the first anti-angiogenic drug approved by the FDA (Ellis and Kirkpatrick 2005). A number of additional anti-VEGF pathway agents followed, including ramucirumab, a monoclonal antibody that targets VEGFR-2, axitinib, regorafenib, sorafenib, sunitinib, vandetanib, and other small molecule tyrosine kinase inhibitors that block the activity of VEGF receptors, and ziv-aflibercept, a recombinant fusion protein that sequesters multiple ligands in the VEGF family (Tarallo and De Falco 2015; Falcon et al. 2016).

SI-B037 contains an antibody that binds VEGF-A and prevents its interaction with VEGF receptors, thereby inhibiting VEGF-mediated angiogenic signaling. Similar to bevacizumab, SI-B037 is designed to neutralize a key driver of tumor angiogenesis and disrupt the formation and maintenance of tumor vasculature. Given the extensive clinical validation of VEGF inhibition across multiple tumor types, targeting VEGF-A represents a well-established therapeutic strategy for the treatment of cancer.

2.3.2. Rationale for a Bispecific Antibody Targeting PD-1 and VEGF-A

A clear scientific rationale exists for simultaneously targeting the PD-1 and VEGF-A pathways for the treatment of cancer. The rationale for combining immune checkpoint blockade with anti-angiogenic therapy is based on their complementary and potentially synergistic mechanisms of action. VEGF-A is a central regulator of tumor angiogenesis and contributes to the development of an abnormal tumor vasculature characterized by vessel leakiness, poor perfusion, and hypoxia. Neutralization of VEGF-A can promote vascular normalization, improve tumor oxygenation, and facilitate infiltration of effector immune cells into the tumor microenvironment (TME). In parallel, blockade of the PD-1 pathway restores antitumor T-cell activity by reversing T-cell exhaustion and enhancing immune-mediated tumor cell killing.

Beyond its role in angiogenesis, VEGF-A exerts multiple immunosuppressive effects within the TME. VEGF-A has been shown to inhibit dendritic-cell maturation, impair antigen presentation, promote the accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and suppress the trafficking and function of effector T cells (Yang, Yan, and Liu 2018). Consequently, VEGF-A inhibition may remodel the TME toward a more immunostimulatory state and increase susceptibility to PD-1 blockade. Furthermore, vascular normalization may facilitate immune-cell access to tumor tissue and improve delivery of therapeutic agents, thereby amplifying antitumor immune responses. Reduction of tumor hypoxia may also attenuate hypoxia-driven immunosuppressive pathways, including the upregulation of immune checkpoint molecules and recruitment of suppressive myeloid populations, creating conditions more favorable for effective antitumor immunity.

The combination of PD-1 blockade and VEGF-A inhibition has the potential to overcome resistance mechanisms that limit the efficacy of either approach alone. VEGF-driven immune exclusion, impaired T-cell infiltration, dysfunctional antigen presentation, and myeloid-dominant tumor microenvironments are recognized mechanisms of primary resistance to immune checkpoint inhibition and may be mitigated through VEGF-A blockade. Conversely, reinvigoration of exhausted CD8+ T cells following PD-1 inhibition can increase production of interferon-gamma (IFN γ), which has been associated with additional vascular normalization and enhancement of antitumor immune responses, supporting a bidirectional interaction between angiogenic and immune regulatory pathways (Qian et al. 2023).

Tumor-induced angiogenesis is highly dysregulated compared with physiologic angiogenesis and results in structurally abnormal blood vessels characterized by poor pericyte coverage, increased permeability, and inefficient perfusion (Morikawa et al. 2002). The interplay between aberrant tumor vasculature and immunosuppressive immune-cell populations establishes a self-reinforcing cycle that promotes tumor progression and limits effective antitumor immunity. VEGF-A contributes directly to this process through the recruitment and expansion of Tregs, MDSCs, tumor-associated macrophages, and other immunosuppressive cell populations that further support angiogenesis and tumor growth (Chen et al. 2021). This reciprocal relationship impairs T-cell trafficking, reduces effector T-cell function, and contributes to immune evasion (Argentiero et al. 2020; Fukumura et al. 2018). Simultaneous inhibition of VEGF-A and PD-1 signaling therefore represents a rational strategy to disrupt both angiogenic and immune-mediated drivers of tumor progression.

Substantial clinical evidence supports the therapeutic synergy between VEGF-A inhibition and PD-1/PD-L1 blockade. Multiple studies evaluating anti-VEGF therapies in combination with PD-1 or PD-L1 inhibitors have demonstrated clinically meaningful benefit across several tumor types. The IMpower150 study established the benefit of combining atezolizumab, bevacizumab, carboplatin, and paclitaxel as first-line treatment for metastatic nonsquamous NSCLC (Socinski et al. 2018), while atezolizumab plus bevacizumab improved outcomes in unresectable hepatocellular carcinoma. Additional evidence from PD-1-based combinations, including pembrolizumab- and camrelizumab-containing regimens, has further validated the biological and clinical synergy between VEGF-A inhibition and PD-1 pathway blockade. Building on this clinical foundation, bispecific antibodies that simultaneously engage VEGF and PD-1/PD-L1 are now being evaluated in clinical development. This unified molecular format offers potential advantages over traditional doublet combinations, including improved pharmacokinetics,

enhanced tumor penetration, and coordinated engagement of both targets within the tumor microenvironment. Bispecific approaches in this space represent a rational evolution of combination therapy, consolidating validated synergistic targets into a single therapeutic agent. Collectively, these findings support a therapeutic strategy that simultaneously neutralizes VEGF-mediated angiogenic and immunosuppressive signaling while restoring PD-1-regulated T-cell function, potentially resulting in more robust and durable antitumor responses than either mechanism alone.

2.3.3. Tumor Indication(s)

IO-Naïve NSCLC with PD-1 activity

Worldwide, there are over 2.4 million new cases of lung cancer annually, with NSCLC representing about 85% to 90% of those cases. Lung cancer (both small cell and non-small cell) is the second most common cancer in both men and women in the United States (US). Approximately 195,000 new NSCLC cases are diagnosed each year in the US (American Cancer Society 2026b). NSCLC has an overall 5-year relative survival rate of roughly 29.5% with standard of care (SoC) indicating a high unmet medical need for this indication (American Journal of Managed Care 2022). The SoC for unresectable, locally advanced NSCLC is concurrent chemotherapy and radiation therapy. This is typically followed by a year of consolidation immunotherapy with durvalumab to improve OS.

Advanced metastatic NSCLC treatment is dictated by the tumor's genetic makeup and biomarker expression. If an actionable mutation is found, oral targeted therapies (tyrosine kinase inhibitors, [TKIs]) are the preferred first-line treatment. For patients without targetable mutations, treatment is guided by activity of the PD-1 immune checkpoint pathway, with PD-L1 expression serving as a predictive biomarker for response to PD-1-directed therapies. Patients with high PD-L1 expression may receive PD-1 inhibitor monotherapy (eg, pembrolizumab), while others are treated with a combination of a PD-1 inhibitor and platinum-doublet chemotherapy (Di Federico et al. 2021).

IO-Exposed NSCLC with PD-1 and VEGF-A activity

In IO-exposed disease, the rationale for dual targeting is to overcome resistance to prior checkpoint inhibitors such as PD-1/PD-L1 immunotherapy while also suppressing pathways that support tumor growth and immune escape (Wu et al. 2025). This makes IO-exposed NSCLC a relevant population for study of PD-1 and VEGF-A–directed treatment (Wu et al. 2024; Wu et al. 2025).

For patients with IO-exposed NSCLC, treatment options after prior immunotherapy are limited, particularly for patients whose disease has progressed following anti-PD-1, anti-PD-L1, or other IO-based regimens. This population includes patients who may have received prior IO therapy in any line of treatment and who now require additional effective therapy after development of resistance or progression. The investigational regimen in this setting targets PD-1 and VEGF-A, with the goal of combining immune modulation and anti-angiogenic activity in a previously treated population (Wu et al. 2024; Wu et al. 2025).

IO-Exposed melanoma with PD-1 and VEGF-A activity

Melanoma is the most serious form of skin cancer and affects adults of all ages. In the US, incidence has increased substantially over the past several decades, although rates have begun to stabilize in some younger populations. In 2026, it is estimated that approximately 104,930 new cases of melanoma will be diagnosed and about 8,430 deaths will occur, with the highest incidence observed in individuals aged 65 years and older (American Cancer Society 2026a). Treatment includes excision of the primary tumor with surrounding tissue and sentinel lymph node biopsy for staging. More extensive lymph node surgery may be performed if nodal metastases are present, and deeper or more advanced tumors may be treated with immunotherapy, radiation, surgery, and/or chemotherapy. Advanced disease is often managed with palliative surgery, immunotherapy, chemotherapy, and sometimes radiation therapy (National Cancer Institute 2026).

The 5-year relative survival rate is 91% overall, with 84% diagnosed at a localized stage. Five-year survival is 98% for localized disease, 63% for regional disease, and 16% for distant disease (Sites 2014). Historically, chemotherapy produced responses in only 10% to 20% of patients with stage III or IV melanoma and did not improve OS, which was about 7 months (American Cancer Society 2014). BRAF and MEK inhibitors improved outcomes, but responses were generally less than 1 year (Flaherty, Robert, et al. 2012; Sosman et al. 2012). Dabrafenib plus trametinib achieved an objective response rate (ORR) of 76% and a PFS of 9.4 months, but resistance remains a limitation (Flaherty, Infante, et al. 2012).

Pembrolizumab and nivolumab are approved for metastatic melanoma and have improved response and survival outcomes versus older comparators (Bristol-Myers Squibb Company 2025; Merck & Co 2026). In ipilimumab-naïve metastatic melanoma, pembrolizumab improved OS and PFS versus ipilimumab, with ORRs of 33% and 34% versus 12% (Merck & Co 2026). In patients who progressed after ipilimumab, pembrolizumab improved PFS versus chemotherapy, with ORRs of 21% and 25% versus 4%. Nivolumab improved OS, PFS, and ORR versus dacarbazine in BRAF V600 wild-type unresectable or metastatic melanoma (Bristol-Myers Squibb Company 2025). In a separate trial, nivolumab alone or with ipilimumab improved PFS versus ipilimumab alone, with ORRs of 40% and 50% versus 14%, respectively.

Despite these advances, there remains an unmet need to improve disease control and OS in metastatic melanoma, both frontline and after progression on ipilimumab or approved anti-PD-1/L1 therapy.

Ovarian Cancer with PD-1 and VEGF-A activity

Ovarian cancer is the fifth most common cancer among women, with an estimated 20,890 new cases and 12,730 deaths expected in the US in 2025 (American Cancer Society 2026a). Ovarian cancer is a heterogeneous group of malignancies with different cell origins and biologic behaviors, and epithelial ovarian carcinoma is the most common clinical subtype (National Cancer Institute, 2025). Standard treatment for ovarian carcinoma typically includes surgery, often with debulking surgery, followed by chemotherapy. PARP inhibitors are used in selected patients as part of first-line maintenance therapy and in other biomarker-directed treatment approaches, including patients with breast cancer gene (BRCA)-mutated disease (Ghisoni et al. 2024).

High-grade serous ovarian cancer is aggressive, frequently presents with peritoneal spread, and often recurs despite response to initial platinum-based therapy (Lisio et al. 2019). Standard treatment for advanced disease includes cytoreductive surgery, platinum-taxane chemotherapy, and in selected patients maintenance therapy with agents such as bevacizumab or poly ADP ribose polymerase (PARP) inhibitors (Lisio et al. 2019). Even with these approaches, long-term outcomes remain poor for many patients, creating a need for new therapies that can target both the tumor and its supportive microenvironment.

A therapeutic approach targeting both PD-1 and VEGF-A is biologically attractive in ovarian cancer because ovarian tumors commonly exhibit immune evasion and a highly angiogenic tumor microenvironment. VEGF-driven angiogenesis is a hallmark of ovarian cancer and contributes to tumor growth, metastatic dissemination, ascites formation, and poor clinical outcomes (Liang et al. 2015; Kawczak and Bączek 2026). Beyond its role in neovascularization, VEGF-A promotes an immunosuppressive tumor microenvironment by impairing dendritic-cell maturation, limiting T-cell infiltration, and supporting the accumulation of regulatory immune-cell populations.

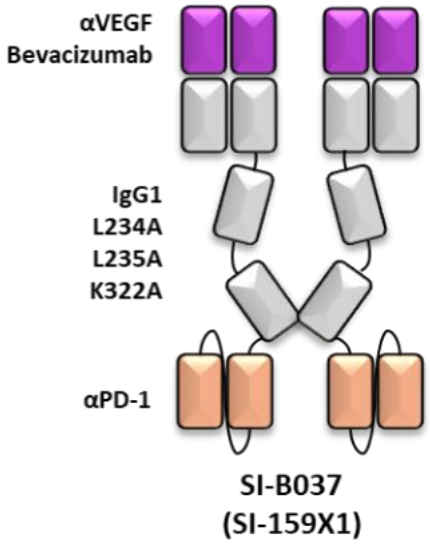
Immune checkpoint signaling through the PD-1/PD-L1 pathway has also been implicated in ovarian cancer immune escape. Expression of PD-L1 within the tumor microenvironment and evidence of T-cell exhaustion suggest that blockade of PD-1 may enhance antitumor immune responses in a subset of patients (Abiko et al. 2015). Although single-agent immune checkpoint inhibition has demonstrated limited activity in unselected ovarian cancer populations, preclinical and clinical evidence supports a mechanistic interaction between angiogenesis and immune suppression.

Consequently, the combination of VEGF-A inhibition and PD-1 blockade may provide complementary antitumor activity by simultaneously normalizing tumor vasculature, enhancing immune-cell trafficking into the tumor, relieving VEGF-mediated immunosuppression, and restoring T-cell effector function. Targeting these interconnected pathways may therefore address 2 key mechanisms of tumor progression and therapeutic resistance in ovarian cancer.

2.4. Investigational Product: SI-B037

SI-B037 is a bispecific antibody that binds to and inhibits the activity of VEGF-A and PD-1

Figure 1 Schematic Diagram of the Structure of SI-B037



Abbreviations PD-1= programmed cell death- 1; GS=glycine + serine; scFv=single-chain variable fragment; VEGF-A =vascular endothelial growth factor A

2.4.1. Nonclinical Safety Results

The SI-B037 safety package utilized New Approach Methodologies (NAMs), meaning human-cell-based and human-tissue-based in vitro assays together with quantitative exposure modeling, rather than a traditional repeat-dose toxicology study in rodents and non-human primates. This approach was taken because SI-B037 combines 2 already-validated binding domains without introducing a new target, a new Fc mechanism, or a new route of administration, it introduces no new molecular or mechanistic uncertainty that a repeat-dose non-human primate study would be needed to resolve. The VEGF-A arm is bevacizumab, an FDA-approved antibody with 2 decades of clinical safety experience; the PD-1 mechanism is defined by approved PD-1 antibodies such as nivolumab and pembrolizumab; the dual VEGF-A × PD-1 mechanism itself has been characterized clinically by the same-class bispecific ivonescimab; and the FcRn interface that governs half-life is left unaltered.

Toxicology characterization of SI-B037 focused on a set of human-relevant in vitro and organ-on-chip studies, structured to answer the 4 hazard questions that drive risk-benefit for a VEGF-A × PD-1 bispecific: cytokine release, hepatic safety, renal safety, and pulmonary safety. No animal single dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, or reproductive toxicity studies were conducted, consistent with the FDA-agreed nonclinical plan for this molecule and stage. Every NAM endpoint was run alongside clinically used comparator antibodies (pembrolizumab, bevacizumab, ivonescimab, and the Fc-PD-1 binding subunit SI-

159FS3), so each SI-B037 readout sits in a comparator-anchored reference frame rather than in isolation.

Cytokine release was characterized for SI-B037 in two independent ten-donor human PBMC cytokine release assays. These assays demonstrated that SI-B037 had no significant effect on cytokines assessed and results were similar to that observed with bevacizumab, ivonescimab, and pembrolizumab.

Liver, kidney and lung tissue toxicity was examined using 3 organ-on-chip studies (Liver-Chip SI-IO-1852, Kidney-Chip SI-IO-1851, Lung-Chip SI-IO-1853) run on the Emulate microphysiological platform. The Liver-Chip shows a mild, comparator-aligned functional hepatic signal with ALT below the bevacizumab signal and no overt hepatocellular injury; the Kidney-Chip shows the expected mild class-effect renal stress signal of VEGF-A pathway inhibition without barrier breakdown; and the Lung-Chip shows no SP-D elevation and no structural disruption, directly addressing the checkpoint-class pneumonitis concern.

The results from the cytokine release assay and tissue chip toxicity studies did not identify any new, severe, or unexpected organ toxicity attributable to the bispecific format of SI-B037 as distinct from its 2 individually well-characterized binding mechanisms or from the close class precedent ivonescimab. The functionality of SI-B037 to neutralize VEGF activity and block PD-1 binding with PD-L1 was demonstrated in cell-based assays. In a cell-based PD-1/PD-L1 reporter bioassay. SI-B037 blocked PD-1 activity in a concentration-dependent manner with an EC50 of 23.08 nM which was comparable to pembrolizumab (EC50 30.54 nM), which was tested in parallel. SI-B037s ability to block PD-1 activity was found to be unaffected by the presence of VEGF.

The ability of SI-B037 to neutralize VEGF activity was demonstrated in a primary human umbilical vein endothelial cell proliferation assay (Study SI-IO-1762), in which VEGF drives endothelial cell proliferation. In this assay SI-B037 displayed an activity (EC50=55.95) similar to the observed with bevacizumab (EC50=54.76). Anti-PD-1 had no effect in the assay demonstrating that inhibition of cellular proliferation was related to VEGF neutralization.

The antitumor activity of SI-B037 was evaluated in 2 independent humanized (PBMC-reconstituted) mouse xenograft models: a human non-small cell lung cancer (NSCLC) model using H1299 cells (Study DT2025PD241) and a human colon cancer model using RKO cells (Study DT2025PD242). In both studies, NOG mice were inoculated with tumor cells, then engrafted with human PBMCs, and once tumors reached approximately 95-125 mm^3 were dosed once weekly for 3 weeks by intravenous injection with SI-B037 at 12, 24, 60, or 100 mg/kg, or with vehicle.

In the H1299 lung cancer model, mean tumor volume on Day 21 was 2584.3 mm^3 in the vehicle group, compared with 1256.0, 1272.7, 1206.2, and 1364.1 mm^3 in the 12, 24, 60, and 100 mg/kg SI-B037 groups, respectively. Each SI-B037 dose group was statistically significantly different from vehicle ($p < 0.05$), corresponding to tumor growth inhibition (TGI) values of 47.4% to 51.5%. In the RKO colon cancer model, mean tumor volume on Day 21 was 1389.0 mm^3 in the vehicle group compared with 908.7, 734.1, 705.8, and 840.0 mm^3 in the 12, 24, 60, and 100 mg/kg groups, corresponding to TGI values of 35.3% to 49.6%, with statistically significant reductions at 24, 60, and 100 mg/kg. In both models, TGI did not increase further at higher

doses, consistent with the lower end of the tested dose range already producing near-maximal pharmacologic effect under these experimental conditions.

2.5. Assessment of Risks and Benefits

2.5.1. Risk Summary and Mitigation Strategy Assessment

The safety profile of SI-B037 will be evaluated in this study. See the Investigator Brochure for further safety and risk details.

Based on the nonclinical studies of SI-B037 (Section 2.4.1) and the known safety profiles of marketed anti-VEGF-A and anti-PD-1 therapies, including ivonescimab, bevacizumab, pembrolizumab, nivolumab, cemiplimab, and dostarlimab, the important potential risks and toxicities associated with SI-B037 are anticipated to include adverse events related to VEGF-A inhibition and immune-mediated adverse events associated with PD-1 blockade. Potential dose modification and management strategies for treatment-related toxicities are provided in Section 6.6 and Appendix 8.

Clinical experience with ivonescimab, a bispecific antibody targeting PD-1 and VEGF-A, has demonstrated a safety profile generally consistent with the known toxicities of VEGF pathway inhibition and PD-1 blockade. Reported TRAEs have included hypertension, proteinuria, hemorrhagic events, hepatic laboratory abnormalities, thyroid dysfunction, rash, pruritus, infusion-related reactions (IRRs), and immune-mediated adverse reactions. Serious adverse events (SAEs) associated with VEGF inhibition and immune checkpoint blockade have also been reported, including pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, severe cutaneous reactions, thromboembolic events, and other clinically significant immune-mediated toxicities. Therefore, similar toxicities may occur with SI-B037 and will be closely monitored throughout the study.

Potential risks associated with VEGF-A inhibition may include hypertension, proteinuria, hemorrhage, thromboembolic events, impaired wound healing, and gastrointestinal perforation or fistula formation. Potential risks associated with PD-1 blockade may include immune-mediated adverse reactions affecting various organ systems, including but not limited to pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and dermatologic toxicities.

No clinical safety information is currently available for SI-B037.

2.5.2. Benefit Summary

Clinical experience with PD-1 inhibitors and VEGF-A inhibitors has demonstrated meaningful therapeutic benefit across multiple advanced solid tumors. SI-B037 combines these 2 validated therapeutic approaches in a single bispecific antibody. Nonclinical pharmacology studies demonstrated preserved functional activity of both binding arms, with activity comparable to approved antibodies targeting the respective pathways. In humanized xenograft models of NSCLC and colorectal cancer, SI-B037 demonstrated statistically significant inhibition of tumor growth compared with vehicle across multiple dose levels, providing evidence of meaningful in vivo antitumor activity. Pharmacokinetic studies demonstrated dose-proportional exposure without meaningful accumulation following repeated dosing, while specificity and comparability studies confirmed selective target engagement and comparable pharmacologic properties

between the clinical and research-grade materials. Collectively, these nonclinical findings support the scientific rationale for the clinical evaluation of SI-B037 in patients with advanced or metastatic solid tumors who have progressed following standard therapies and continue to have a significant unmet medical need.

2.5.3. Overall Risk-Benefit Assessment

There remains a high unmet need for better treatment options for participants with previously treated locally advanced and metastatic melanoma, NSCLC, ovarian cancer, and other solid tumor types. Considering the available nonclinical safety data supporting FIH dosing of SI-B037, the established pharmacologic rationale and clinical experience with VEGF-A and PD-1 pathway inhibition, and the protocol-defined risk-mitigation measures, the anticipated risks associated with SI-B037 are considered justified by the potential clinical benefit that may be afforded to eligible participants.

3. TRIAL OBJECTIVES

Table 4 Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the safety and tolerability of SI-B037 in participants with solid tumors who have received at least one prior line of therapy for advanced disease	• SAEs, adverse events of special interest (AESI), TEAEs, death, TEAE leading to discontinuation, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters (including the change-from-baseline ECG parameters: HR; PR, QTcF, and QRS intervals [ΔHR, ΔPR, ΔQTcF, and ΔQRS])
• To determine recommended dose for expansion (RDE), the MSED if reached or MAD of SI-B037	• DLTs
Secondary	
• To evaluate preliminary efficacy	• Objective Response Rate (ORR), Disease Control Rate (DCR), Progression-free survival (PFS), Overall survival (OS)
• To evaluate the pharmacokinetic characteristics of SI-B037	• Pharmacokinetic (PK) parameters: C_{max}, T_{max}, $T_{1/2}$, $AUC_{0-t,}$ CL, and C_{trough}, etc.
Exploratory	
• To evaluate the immunogenicity of SI-B037	• Immunogenicity: incidence of anti-drug antibodies (ADAs) to SI-B037
• To identify biomarkers that correlate with SI-B037 response or toxicity	• To determine biomarkers obtained before and/or after treatment and/or during disease progression in archived and/or fresh tumor tissue and blood samples (eg, PD-1, VEGF-A and other soluble proteins)

4. TRIAL DESIGN

A schema of the SI-B037-ST-101 trial is provided in Section 1.2.

4.1. Description of Trial Design

This is a multicenter Phase 1 open-label study to evaluate the safety, tolerability, pharmacokinetic profile, and initial efficacy of SI-B037 in subjects with locally advanced or metastatic solid tumors for which no standard treatment is available, including but not limited to participants who have been diagnosed with NSCLC, melanoma, and ovarian cancer.

This study has 3 parts:

- Part A: Dose Escalation (Section 4.1.1); approximately 18 participants
- Part B: Dose Finding (Section 4.1.2); approximately 60 participants
- Part C: Dose Expansion (Section 4.1.3); approximately 320 participants

Approximately 400 male or female subjects, ≥18 years of age with locally advanced or metastatic solid tumors who have failed at least 1 line of standard therapy in the advanced/metastatic setting or are unable to receive standard treatment will be enrolled into the study. A high-level schema of Study SI-B037-ST-101 is shown in Section 1.3

4.1.1. Part A: Dose Escalation

Beginning with Cycle 1, SI-B037 will be administered on Day 1 by intravenous (IV) infusion every 3 weeks (D1Q3W) (Table 5).

Table 5 Dose Escalation Doses

Dose level	Day 1 Dosage (D1Q3W) (21-day cycles)
1	3 mg/kg
2	9 mg/kg
3	20 mg/kg

Abbreviations: D1Q3W=Day 1 every 3 weeks (1 cycle); IV=intravenous.
Intermediate doses may be considered based on review of available safety, tolerability, and PK data in this and other studies with the investigational product

Dose escalation will begin with a BOIN design and proceed until the maximum tolerated dose (MTD) or minimum safe and pharmacologically effective dose (MSED) is reached.

The DLT observation period is defined as the initial 21 days of Cycle 1. A DLT-evaluable participant is defined as a participant who has received at least 1 dose of SI-B037 and has either completed the DLT observation period or experienced a DLT during the DLT observation period. In dose escalation portion of the study, participants who are not DLT-evaluable will be replaced.

Recommended dose(s) for Part C/dose expansion (RDE) candidate will be selected by the sponsor in collaboration with the Safety Monitoring Committee (SMC) which is composed of study investigators and sponsor representatives. The decision to dose escalate will be selected based on the totality of evidence including PK, PD, safety, tolerability, and activity.

Participants with a primary diagnosis of lung cancer (including non-small cell lung cancer [NSCLC], small cell lung cancer, and other thoracic pulmonary malignancies) are excluded from Part A (dose escalation) of the study.

Bayesian Optimal Interval (BOIN) Design

Dose escalation will be guided by the BOIN design to find the MTD based on observed DLTs (Liu and Yuan 2015b; Yuan et al. 2016). The computation is implemented by the software "BOIN" available at http://www.trialdesign.org. The target toxicity rate for the MTD is $\phi = 0.25$ and the sample size is approximately 18 DLT-evaluable participants. The BOIN design uses the following rule, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.167, escalate the dose to the next higher dose level;
- If the observed DLT rate at the current dose is > 0.334, de-escalate the dose to the next lower dose level;
- Otherwise, stay at the current dose

The rule is optimized to minimize the probability of incorrect dose assignment under alternative hypotheses $\phi_1 = 0.1$ (underdosing) and $\phi_2 = 0.43$ (overdosing). The decision-making flowchart for escalation (E), staying (S) at the current dose, dose de-escalation (D) to the previous or an intermediate dose, and dose de-escalation with dose elimination (DE) of current and higher doses, based on the number of participants treated and the number of toxicities (DLTs) observed at a given dose level is provided in Figure 4.The decision will be made by the sponsor in collaboration with the SMC (Section 4.2.5) according to the BOIN escalation rules (Section 4.2.3).

Participants will be enrolled and treated in cohorts of 3 to 6 participants during the dose escalation part. The dose escalation will stop if the number of participants treated at the current dose reaches 12 and the decision by the sponsor and SMC according to Figure 4 is to retain the current dose. After the dose escalation part is completed, the MTD is determined based on isotonic regression, and the MTD is selected as the dose where the isotonic estimate of the toxicity rate is closest to the target toxicity rate (Liu and Yuan 2015a). If there are ties, the higher dose level will be selected when the isotonic estimate is lower than the target toxicity rate and the lower dose level will be selected when the isotonic estimate is greater than or equal to the target toxicity rate.

The actual number of subjects enrolled and dose levels to be explored in this study will depend on the MTD and/or RDE based on DLTs reported during the DLT observation period.

4.1.2. Part B: Dose Finding

In Part B/dose finding, approximately 60 subjects may be enrolled (up to 20 subjects at each single dose level). However, the actual number of subjects enrolled depends on the numbers of dose levels studied, any expansions within a dose level (up to 20 subjects with any expansion within a single dose level), and any subject replacement required to complete a dose level.

After each dose level completes its individual DLT observation period and the sponsor and SMC determine that further dose escalation is safe, the study will proceed to the dose finding phase. In

this phase, approximately 20 participants will receive SI-B037 at one of the following dose levels: 3 mg/kg, 9 mg/kg, or 20 mg/kg. The objective of dose finding is to confirm the tolerability of SI-B037 at these candidate RDEs. In conjunction with the SMC the sponsor will ultimately select recommended dose for Part C (dose expansion) based on the totality of evidence including PK, PD, safety, tolerability, and activity.

Guidelines for dose modifications such as dose reductions, delays, and permanent discontinuations are provided in Section 6.6.

During the dose finding, enrollment will be carefully monitored based on the occurrence of TRAEs that meet DLT criteria for each selected RDE candidate. The incidence and nature of TRAEs observed at each dose level during the dose finding part will be evaluated as part of the overall benefit-risk assessment. The sponsor, together with the SMC, will review the safety data and may determine that an RDE candidate is not tolerable.

Enrollment may be stopped at that dose level, and a lower dose will be selected for further exploration in Part C. This gating mechanism ensures that only doses that demonstrate an acceptable safety profile and tolerability are continued in the study, safeguarding the well-being of the enrolled participants.

4.1.3. Part C: Dose Expansion

Upon completion of dose escalation and, when applicable, dose finding, dose expansion will begin, with the objectives to (1) confirm the safety of SI-B037 at the RDEs, (2) evaluate preliminary efficacy in participants with locally advanced or metastatic tumors, and (3) determine the dose that shows the best risk-benefit balance.

During the dose expansion phase, excessive toxicities will be carefully monitored. The stopping rules using the Bayesian Toxicity Monitoring (BTM) method will be applied. Once the stopping boundary is crossed, a comprehensive data review will be performed. The enrollment may be paused upon the evaluation of the totality data. The details of the stopping boundaries are included in Appendix 9.

Participants will be assigned as follows:

- Participants will be selected based on their tumor type and then randomized into 1 of 2 dose cohorts. Up to 40 participants may be enrolled in each dose cohort within each tumor type, for a total of up to 80 participants per tumor type. Participants will be treated in the following manner:SI-B037 dose level: (1) RDE1 or (2) RDE2 D1Q3W and into each of the following sub-cohorts.
  - IO-Naïve NSCLC
  - IO-Exposed NSCLC
  - IO-Exposed melanoma
  - Ovarian cancer

In each cohort in Part C, futility analysis will be performed using the Simon 2-stage design. Refer to Section 9.3.4 for details (Simon 1989).Rationale for Trial Design

This is a dose range finding study and will determine the MSED, the maximum administered dose (MAD) that may or may not be the MTD, and RDE.

Dose levels have been selected based on the nonclinical pharmacology, pharmacokinetic, and toxicology data generated for SI-B037, including antitumor activity observed in humanized xenograft models, demonstrated functional activity against PD-1 and VEGF-A, projected human pharmacokinetics, and the human-relevant toxicology data generated under the FDA-agreed NAM strategy.

The dose and dosing schedule used in this study were also informed by the clinical experience with approved antibodies targeting the PD-1 and VEGF pathways, including pembrolizumab, nivolumab, and bevacizumab (Freshwater et al. 2017; Hurkmans et al. 2019; Han et al. 2016). Consistent with the demonstrated intact FcRn-mediated recycling and projected IgG-like pharmacokinetic profile of SI-B037, the selected dosing interval is expected to provide sustained systemic exposure throughout the dosing period.

The Q3W dosing interval was selected based on the projected human pharmacokinetic profile of SI-B037. In nonclinical studies, SI-B037 demonstrated intact FcRn-mediated recycling and conventional IgG-like pharmacokinetic characteristics, with a projected human terminal half-life of approximately 14-21 days.

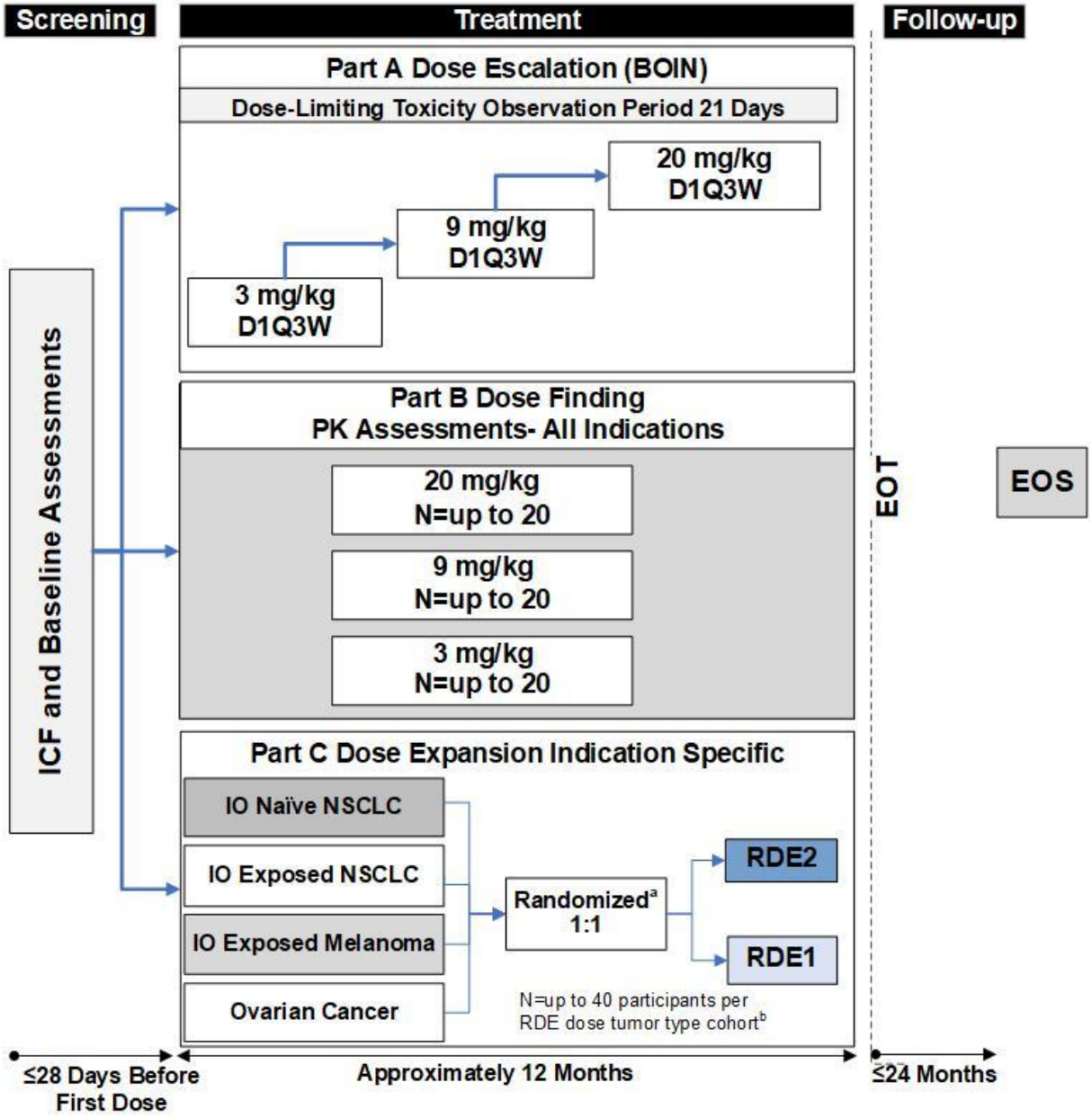
Dose escalation will proceed until the MTD, MAD, or MSED is reached, as defined in the protocol.

4.2. Overall Design

4.2.1. Study Schema

The study schema is provided in Figure 2.

Figure 2 Study Schema



Abbreviations: BOIN= Bayesian Optimal Interval; D1Q3W=day 1 every 3 weeks; EOS=end of study; EOT=end of treatment; ICF=informed consent form; IO=Immuno-Oncology; OC=ovarian cancer; NSCLC=non-small cell lung cancer; PK=pharmacokinetics

a. Participants for each tumor cohort will be randomized to receive either RDE1 or RDE2
b. Up to 80 participants per tumor type will be randomized to receive SI-B037 at either RDE1 or RDE2

*Note: RDE1 is the lower dose that will be chosen for expansion, also known as Dose -1. RDE2 will be the RP2D and the higher dose chosen for expansion.

4.2.2. Starting Dose Rationale

An extensive review of relevant agents in clinical development within the same therapeutic class, including PD-1, VEGF-A, and VEGF-A/PD-1 inhibitors with established clinical safety and efficacy profiles, supports the expectation that SI-B037 may achieve meaningful biological activity at dose levels that remain well tolerated.

A starting dose of 3 mg/kg, based on the minimal anticipated biological effect level (MABEL), could accelerate the dose escalation of SI-B037 to an efficacious dose. This dose is lower than MABEL (4.58 mg/kg), taking into consideration the anticipated mechanism of action and safety profile, and corresponds to a biologically meaningful "entry into activity" dose. Initiating dose escalation at this level is intended to minimize patient exposure to potentially sub-therapeutic doses while maintaining an acceptable safety margin. This approach is justified in an oncology population with advanced malignancies, where prolonged exposure to ineffective doses may confer limited clinical benefit.

The recommended starting dose for SI-B037 in this study is 3.0 mg/kg D1Q3W, which is significantly below the recommended dose for ivonescimab (PD-1 × VEGF bispecific antibody)[20 mg/kg]. Notably, PD-1 inhibitors and VEGF inhibitors have not reached MTDs during their respective clinical development programs and have been readily combined with multiple other therapeutic classes.

Consequently, selection of a starting dose of 3 mg/kg may facilitate an efficient dose escalation toward potentially active dose levels while maintaining an appropriate safety margin.

In the FIH Phase 1a study of ivonescimab (a PD-1 × VEGF bispecific antibody that combines immune checkpoint inhibition with anti-angiogenic activity), dose escalation was initiated at 0.3 mg/kg, and no dose-limiting toxicities were observed across dose levels ranging from 0.3 to 20 mg/kg administered every 2 weeks (Frentzas et al. 2024). Subsequent clinical studies further supported the development of the dual PD-1/VEGF inhibition strategy, demonstrating that concurrent blockade of immune checkpoint and angiogenic pathways could be achieved across a broad exposure range while maintaining an acceptable safety profile.

SI-B037 was evaluated in mice at doses ranging from 12 to 100 mg/kg (human equivalent doses 1mg/kg-8.3mg/kg) for antitumor activity, pharmacokinetic properties, and safety. Across this dose range, SI-B037 produced TGI of approximately 35% to 50% without observable safety concerns, including no adverse effects on body weight.

In addition, no signals of hepatocellular, renal, or pulmonary toxicity were observed in the in vitro safety assessment studies.

Taking into consideration the substantial clinical safety experience with agents targeting VEGF-A and PD-1, the well-characterized toxicity profiles associated with these pathways, and the corresponding risk-mitigation measures incorporated into the FIH clinical study of SI-B037, the proposed starting dose of 3 mg/kg represents a balanced approach. This dose is intended to support participant safety while maximizing the opportunity to detect early signals of clinical activity and minimizing the total number of participants required to characterize the dose-exposure-response relationship. Although this approach differs from traditional FIH dose selection methodologies that rely primarily on conservative toxicology-based starting doses, the

extensive existing knowledge of both molecular targets and the substantial prior clinical experience with VEGF and PD-1 pathway inhibition provide a strong scientific rationale for this strategy. Therefore, the starting dose approach is considered justified for SI-B037.

4.2.3. Dose Escalation Design

The dose escalation will be guided by the BOIN design to find the MTD based on observed (Yuan et al. 2016; Liu and Yuan 2015). The computation is implemented by the software "BOIN" available at http://www.trialdesign.org.

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size is 18. As shown in Figure 3 the BOIN design uses the following rule, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.167, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is > 0.334, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

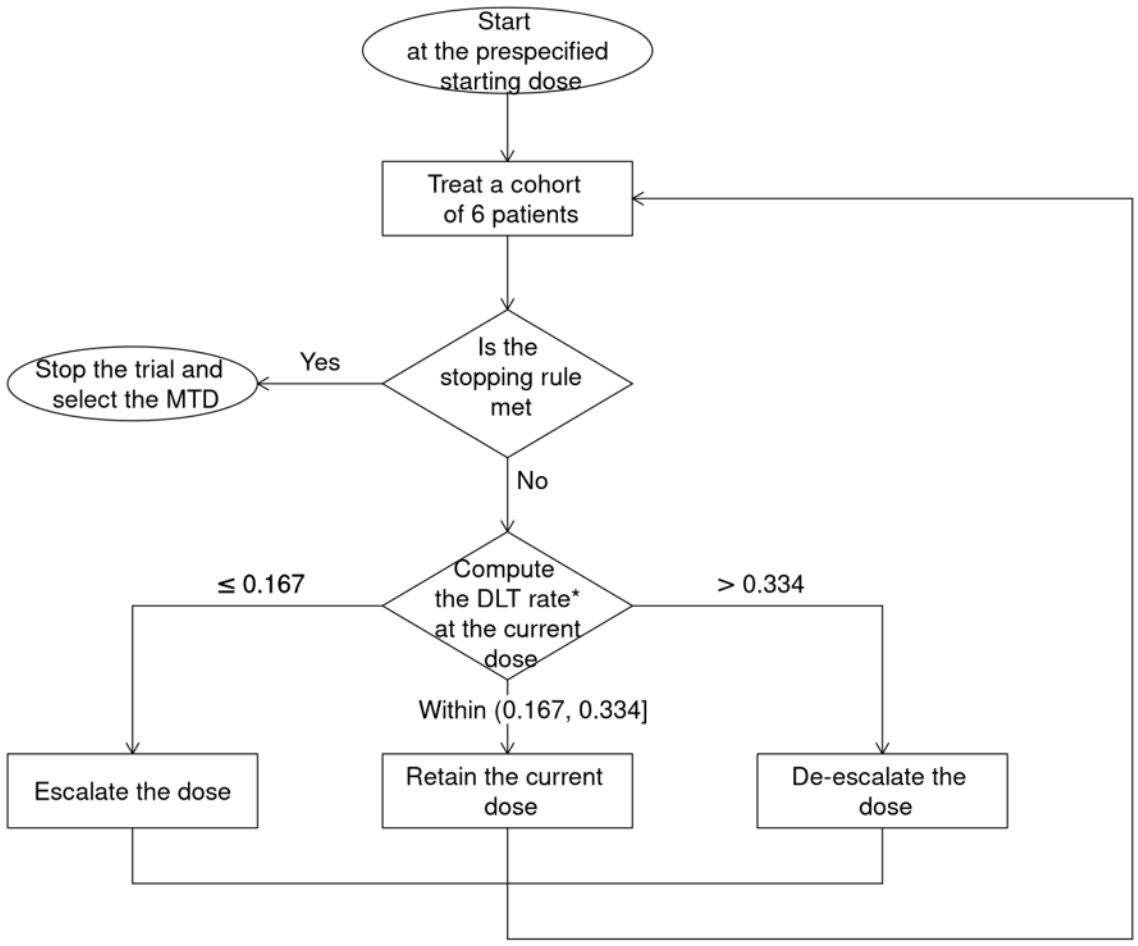
The rule is optimized to minimize the probability of incorrect dose assignment under alternative hypotheses $\phi_1 = 0.1$ (underdosing) and $\phi_2 = 0.43$ (overdosing).

The decision-making flowchart and rules for escalation (E), staying (S) at the current dose, dose de-escalation (D), and DE of current and higher doses, based on the number of subjects treated and the number of DLTs observed at a given dose level are provided in Figure 3 and Figure 4. The decision will be made by the sponsor in collaboration with the SMC (Section 4.2.4) according to the BOIN escalation rules and flowchart.

Subjects will be enrolled and treated in cohorts of 3 to 6 subjects during the dose escalation part. The dose escalation will stop if the number of subjects treated at the current dose reaches 12 and the decision according to Figure 4 is to stay at the current dose. After the dose escalation part is completed, the MTD is determined based on isotonic regression, and the MTD is selected as the dose where the isotonic estimate of the toxicity rate is closest to the target toxicity rate (Liu and Yuan 2015). If there are ties, the higher dose level will be selected when the isotonic estimate is lower than the target toxicity rate and the lower dose level will be selected when the isotonic estimate is greater than or equal to the target toxicity rate.

In this BOIN design, the prior distribution for any given dose level j is $p_j \sim Unif(0,1)$. The overdose control is defined as the posterior probability $\Pr(p_j > \phi | y_j, n_j) > 0.95$, where ϕ is the target DLT rate 0.25, $y_j$is the number of DLTs observed at dose level j, n_j is the number of patients treated at dose level j, and $y_j | n_j, p_j \sim Binom(n_j, p_j)$ is the distribution of the DLT rate.

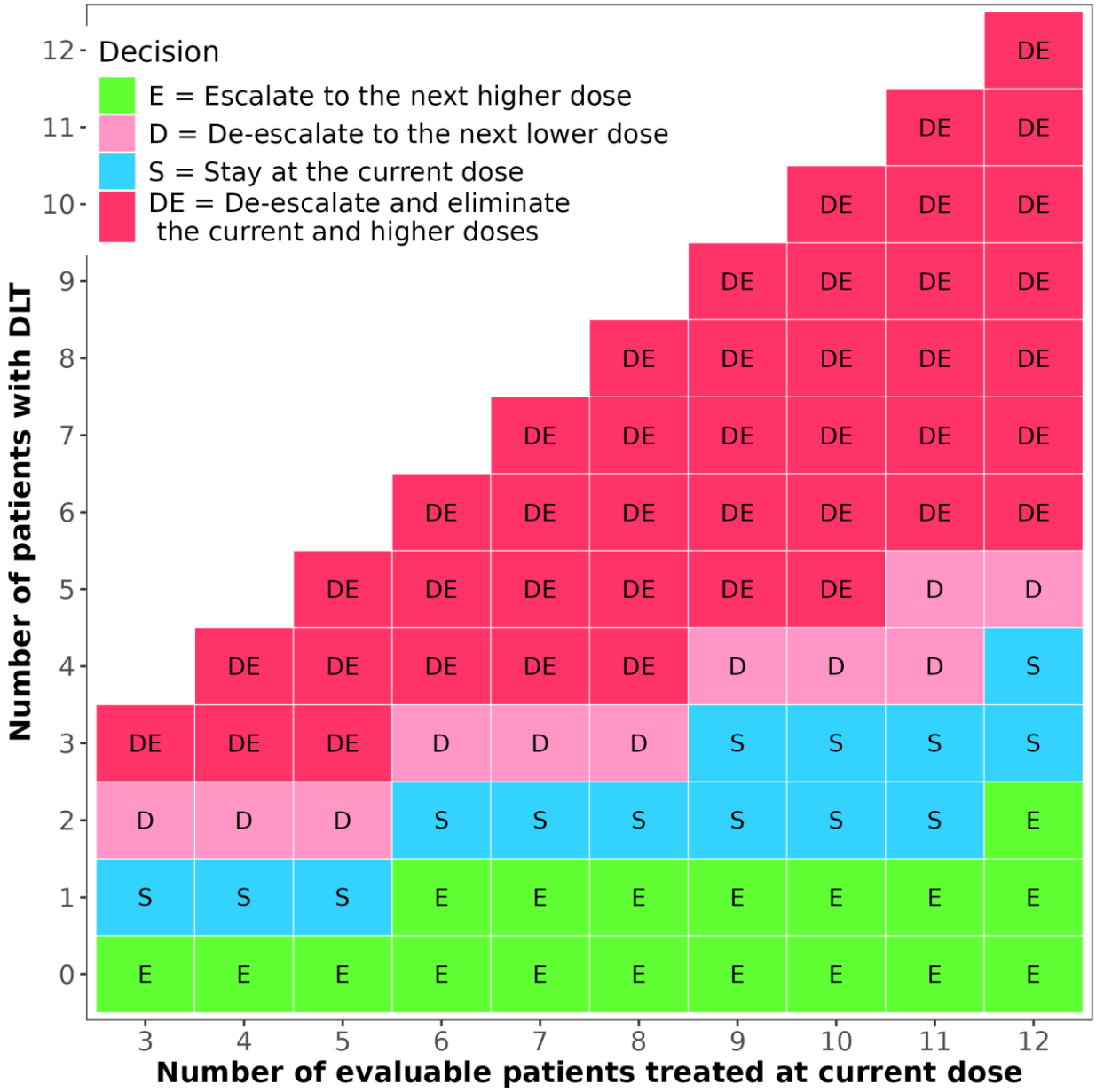
Figure 3 BOIN Design Escalation Flowchart



$$* \text{ DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose.

Figure 4 BOIN Design Escalation Rules



Abbreviation: DLT=dose-limiting toxicity.

NOTE: Evaluable refers to a DLT-evaluable subject, previously defined as a subject who has received at least one dose of SI-B037 and has either completed the DLT observation period or experienced a DLT during the DLT observation period.

4.2.4. Dose Escalation Dose Selection

The rational for the starting dose of 3.0 mg/kg is described in Section 4.2.2. Following the initial dose the next planned dose is 9 mg/kg.

Escalation to the second dose (9 mg/kg) is designed to explore enhanced VEGF pathway modulation while maintaining overlap with known safety and tolerability profiles of

anti-angiogenic therapy. This dose level allows evaluation of incremental biological activity beyond PD-1–dominant effects and supports characterization of PK/PD relationships relevant to VEGF-A inhibition.

The third dose escalation level will target combined PD-1 and VEGF pathway engagement at a higher exposure level (20 mg/kg). This dose is intended to maximize dual-pathway biological activity and to assess the upper range of tolerability for combined immunomodulatory and anti-angiogenic effects. Escalation to this level will proceed only after reviewing cumulative safety, PK, and PD data from prior dose levels, in accordance with protocol-defined escalation criteria.

Dose escalation will follow a standard cohort-based approach, with decisions guided by observed DLTs, overall safety profile, and emerging PK/PD data.

4.2.5. Safety Monitoring Committee

The SMC will comprise all trial investigators/sub-investigators, the sponsor medical monitor, and the clinical scientist; other functional area leads from translational research, pharmacovigilance, biostatistics, clinical operations, and other sponsor representatives will be invited as needed. All principal investigators representing the site with active patients will be invited to attend the meeting. A SMC charter will define the structure, roles, and responsibilities of the SMC and will describe the process for the selection of RDEs.

The decision to escalate to the next dose cohort, expand at that dose level, and/or escalate to an intermediate dose cohort is based on real-time assessment of safety, efficacy, tolerability, pharmacokinetics, and pharmacodynamics data in each cohort for all subjects who have completed the DLT observation period (dose escalation). Some data, such as pharmacokinetics, will be tested in batches and will be assessed as close to real-time as possible.

A notification of the SMC's decision will be issued to sites for each dose level to continue unless further discussion is required.

Dose escalation will proceed according to the rules in Section 4.2.3.

Recommended dose(s) for Part C/dose expansion (RDE) candidate will be selected by the sponsor in collaboration with the SMC based on the totality of evidence including PK, PD, safety, tolerability, and activity. This includes preliminary antitumor and efficacy results from Part A and Part B.

4.2.6. Dose-Limiting Toxicities

The DLT observation period is defined from the first treatment cycle for each dose level to the end of the cycle (the first 21 days of treatment). Toxicities will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE ver. 6.0, Appendix 3).

A DLT is defined as any of the following events that are not clearly due to the underlying disease, disease progression, or extraneous causes:

- Any TEAE of ≥ Grade 3 except those that are clearly and incontrovertibly due to disease progression or extraneous cause

- Toxicity that results in a >14-day delay in treatment
- **Hematologic toxicities**
  - ANC <500/mm³ (<0.5×10⁹/L) lasting >7 days
  - Febrile neutropenia of any grade and any duration
  - Platelets <50,000-25,000 mm3 with significant bleeding or platelets <25,000 mm3 for more than 7 days
  - Grade 4 thrombocytopenia lasting > 72 hours
- **Non-hematologic toxicities**
  - Death not clearly related to disease progression or extraneous cause
  - Hy's law cases
  - Grade 3 or higher infusion-related reactions (IRR) except for a first occurrence of Grade 3 IRR that occurs in the absence of steroid prophylaxis and resolves within 6 hours following appropriate clinical management
  - AST/ALT 5–8× ULN persisting >2 weeks, both regardless of presence of liver metastases
  - Grade ≥3 non-hematologic toxicities, except for:
    - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
    - Grade 3 fatigue for less than 1 week
    - Grade ≥3 electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
    - Grade 3 amylase or lipase not associated with symptoms/manifestations of pancreatitis and does not require hospitalization
    - Grade 3 rash that improves to Grade <3 with standard management within 7 days

No delay in dosing or dose adjustment will be allowed during the DLT observation period unless clinically indicated.

4.2.7. Rationale for Trial Duration

Trial duration is based on estimated time for enrollment for each part of the study as well as the amount of time/cycle duration and safety follow-up.

The estimated study duration by part is as follows:

- Dose Escalation
  - Enrollment is planned to occur over approximately 6 months

  - Treatment and follow-up are projected to be completed approximately 12 months thereafter

- Dose Finding
  - Enrollment is planned to occur over 9 months
  - Treatment and follow-up are projected to be completed approximately 12 months thereafter
- Dose Expansion
  - Enrollment is planned to occur over 18 months
  - Treatment and follow-up are projected to be completed approximately 12 months thereafter

The maximum study duration for each subject participating in the study including the screening period will be 24 months and end of study (EOS) follow-up will be approximately 24 months.

4.3. Trial Stopping Rules

This study or any cohort, dose stage, or phase may be suspended or prematurely terminated by the sponsor at the sponsor's discretion. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study subjects, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB/IEC, and sponsor and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to the study visit schedule.

When a study is prematurely terminated, refer to Section 1.3 for the handling of enrolled study participants.

4.3.1. Individual Subject Discontinuation

Subject discontinuation and withdrawal are described in Section 7.2. In addition, treatment will stop for an individual subject if the subject experiences:

- Disease progression by response evaluation criteria in solid tumors (RECIST) V1.1 without evidence of clinical benefit with continued therapy based on the Investigator's judgment.
- Toxicity requiring discontinuation of investigational product as listed in Table 9.

The sponsor may decide to stop treatment for an individual subject on a case-by-case basis.

The reason for subject discontinuation or withdrawal from the study and the date of this decision must be recorded on the electronic case report forms (eCRF).

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal

of consent. If a subject withdraws from treatment only, further evaluations and survival follow-up are allowed.

4.3.2. Study Stopping Rules

SystImmune has the right to terminate this study or a study site from participating at any time.

Reasons for terminating the study at a specific study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory requirements in conducting the study

Enrollment in the study will stop/pause to assess subject safety if any of the following occur:

- The safety committee recommends termination for safety reasons
- The incidence or severity of AEs in this or other SI-B037 studies indicate a potential health hazard to subjects
- Death (other than disease progression) that is at least possibly related to SI-B037 or indicate a potential health hazard to subjects
- All subjects enrolled in the study have withdrawn from treatment, completed participation in the study, or are lost to follow-up

4.4. Start of Trial and End of Trial

The start of the study is defined as the date the first participant is enrolled in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SOA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SOA for the last participant in the study globally.

Study completion is defined as the completion of the clinical study report.

5. TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

This study will enroll participants with advanced or metastatic solid tumors.

5.1. Inclusion Criteria

1. Signed the informed consent form voluntarily and agreed to follow the trial requirements.
2. Male or Female Age ≥18 years.
3. Has a life expectancy of ≥3 months.
4. Subjects with documented locally advanced or metastatic solid tumor(s) not amenable to curative surgery or radiation and have received at least 1 line of standard therapy in the metastatic setting, or whose cancer is considered refractory to the SoC or for which no standard treatment is available.

   Participants with recurrence or progression occurring during or ≤6 months after completion of neoadjuvant/adjuvant systemic therapy would be considered as having failed 1 line of standard therapy in the metastatic setting and hence be eligible for the trial. At least 1 measurable lesion based on RECIST v1.1
5. At least 1 measurable lesion based on RECIST 1.1
6. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1.
7. Toxicity of previous antitumor therapy has returned to level ≤1 as defined by NCI-CTCAE V6.0 (except for asymptomatic laboratory abnormalities such as elevated ALP, hyperuricemia, elevated serum amylase/lipase, and elevated blood glucose; except for toxicity that the investigator determined to have no safety risk, such as alopecia, Grade 2 peripheral neurotoxicity, hypothyroidism stabilized by hormone replacement therapy, etc.).
8. Has no serious cardiac dysfunction and left ventricular ejection fraction ≥50%.
9. Has adequate organ function, before enrollment defined as:

System	Lab Value
Hematological[a]	
Absolute neutrophil count (ANC)	≥1.5 ×10^9/L
Platelets	≥100×10^9/L
Hemoglobin (Hb)	≥9.0 g/L
Hepatic[b]	
Total bilirubin (TBIL)	≤1.5× upper limit of normal (ULN) ≤3×ULN for participants with Gilbert's syndrome
AST and ALT	≤2.5×ULN without liver metastasis ≤5.0×ULN with liver metastasis
Renal[c]	

Creatinine clearance (CrCl)	≥50 mL/minute
Urine protein	≤2+ **OR** ≤1000 mg/24 hours
Coagulation[d]	
International Normalized Ratio (INR)	≤1.5×ULN
Activated partial thromboplastin time (aPTT)	≤1.5×ULN

a. Blood transfusion, platelet transfusion, erythropoietin (EPO), hematopoiesis agents (such as [TPO]), and G-CSF use are not allowed 1 week prior to Screening
b. For participants with Gilbert's syndrome, conjugated bilirubin ≤1.5×ULN and TBIL ≤3.0×ULN
c. Creatinine clearance (Cockcroft-Gault equation)
d. Unless receiving anticoagulation therapy with PT and aPTT levels within the intended therapeutic range.

10. Sexually active fertile participants and their partners must agree to use highly effective methods of contraception (defined in Appendix 5 of the protocol) during the course of the study and for 4 months for men and 7 months for women after the last dose of study treatment. An additional contraceptive method, such as a barrier method (eg, condom), is recommended.
11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at Screening and must be nonlactating. Female participants are considered WOCBP unless one of the following criteria are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman >45 years old in the absence of other biological or physiological causes. In addition, females <55 years old must have a serum follicle stimulating hormone (FSH) level >40 mIU/mL to confirm menopause.

    NOTE: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.
12. Participants whose tumor has an actionable biomarker(s) for which an US FDA or other country-specific approved targeted therapy exists in the applicable disease setting must have previously received the appropriate targeted therapy and experienced disease progression during or after treatment, unless such therapy was contraindicated, not tolerated, unavailable, inaccessible, or otherwise not considered medically appropriate by the Investigator.

PART C Additional Inclusion Criteria (Dose Expansion Only)

For IO-exposed NSCLC:

13. Histologically or cytologically confirmed unresectable locally advanced or metastatic NSCLC in subjects previously exposed to immune checkpoint inhibitor therapy (IO-exposed), defined as having received at least one prior line of treatment with a PD-1 inhibitor, and/or PD-L1 inhibitor, and/or CTLA-4 inhibitor in combination with a PD-1 inhibitor, and/or other approved immune

checkpoint–modulating agents (as monotherapy or in combination), and whose disease is refractory to SoC therapy or for whom no appropriate standard treatment options are available. In addition, subjects must have received at least one prior line of platinum therapy.

For IO-Naïve NSCLC:

14. Histologically or cytologically confirmed unresectable locally advanced or metastatic NSCLC in subjects with no prior exposure to immune checkpoint inhibitor therapy (IO-naïve), defined as having no prior treatment with a PD-1 inhibitor, PD-L1 inhibitor, CTLA-4 inhibitor, or other approved or investigational immune checkpoint–modulating agent (as monotherapy or in combination). In addition, subjects may have received one prior line of platinum therapy +/-anti-VEGF Mab for locally advanced or metastatic NSCLC and failed the treatment.

For Melanoma:

15. Histologically confirmed unresectable or metastatic melanoma with prior treatment with an immune checkpoint inhibitor therapy (IO-exposed), including a PD-1 inhibitor, and/or PD-L1 inhibitor, and/or CTLA-4 inhibitor in combination with a PD-1 inhibitor, and/or other approved immune checkpoint–modulating agents (as monotherapy or in combination) and documented disease progression following such therapy.

For Ovarian Cancer:

16. Has histologic documentation of epithelial ovarian, primary peritoneal, or fallopian tube cancer that has progressed or relapsed on or after a previous chemotherapy with or without a PARP inhibitor. Prior bevacizumab treatment is allowed.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible for participation in this study:

1. Chemotherapy, biological therapy, immunotherapy, targeted therapy (including small molecule inhibitor of tyrosine kinase), and other antitumor therapy within 4 weeks or 5 half-lives (whichever is shorter) prior to the first administration; radical radiotherapy, major surgery within 4 weeks prior to the first administration; mitomycin and nitrosoureas treatment within 6 weeks prior to the first administration; oral drugs such as capecitabine, or palliative radiotherapy within 2 weeks prior to initial administration.
2. Received systemic immunostimulatory therapy (such as IFN-α, IL-2) within 4 weeks prior to the first dose or is still within 5 half-lives of the treatment (whichever is longer).
3. Received immunosuppressive drugs (such as corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, anti-TNF-α drugs) within 2 weeks prior to the first dose, with the following exceptions: acute low dose systemic

immunosuppressive drug therapy. Participants who are receiving treatment with systemic glucocorticoids >10 mg/day equivalent of prednisone, except for the treatment of chronic obstructive pulmonary disease (COPD), antiemetic, infusion reactions; however, treatment with low dose glucocorticoids (≤10 mg/day equivalent of prednisone) is permitted. The use of topical, inhaled, and locally injected steroids is permitted.

4. Participants with history of severe heart disease, such as symptomatic congestive heart failure Grade ≥2 (CTCAE 6.0), New York Heart Association (NYHA) Grade ≥2 heart failure at any time, history of myocardial infarction, or unstable angina pectoris within 6 months before enrollment.
5. Participants with prolonged QT interval (QTcF >470 msec), complete left bundle branch block, Grade 3 atrioventricular block, or a history of additional risk factors for Torsades de Pointes (TdP; eg, heart failure as defined in Exclusion Criterion 4, chronic or recurrent hypokalemia that requires medical intervention, congenital long QT syndrome, family history of long QT syndrome) or any current concomitant medication known to prolong the QT/QTc interval or cause TdP.
6. Among subjects who have been treated with prior immunotherapy, subjects with prior > Grade 3 irAEs that lead to permanent discontinuation and/or any history of life-threatening irAEs including but not limited to pneumonitis, myocarditis, neurologic autoimmune toxicity; and/or subjects with prior irAEs requiring prolonged immunosuppressive therapy (>12 weeks).

   Note: Subjects who have previously experienced any of the following conditions are permitted to participate: Experienced prior Grade ≤2 irAEs that have resolved to Grade ≤1 or baseline; are off systemic immunosuppression or on physiologic/replacement doses (≤10 mg prednisone equivalent).
7. Grade ≥ 3 toxicity related to anti-angiogenic therapy (except for fever and other toxicities that the investigator believes does not pose a safety risk to trial participants) when receiving anti-angiogenic therapy in the past.
8. Other malignant tumors were diagnosed within 5 years prior to the first administration with the following exceptions: basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or carcinoma in situ after radical resection.
9. For the dose escalation portion of the study only, participants with a primary diagnosis of lung cancer (including NSCLC, small cell lung cancer, and other thoracic pulmonary malignancies) are excluded.
10. Participants with a thromboembolic event (eg, deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 6 months before Screening.
11. Participants with active or recent clinically significant bleeding are excluded:

- Any history of intracranial or spinal hemorrhage (absolute contraindication)
- Any Grade 2+ hemorrhage within 12 months prior to enrollment (including GI, pulmonary, genitourinary, other)
- Active bleeding of any type
    - Unhealed hemorrhagic ulcers
    - Vasculitis with active or recent bleeding

Note: All other bleeding events: Must be >12 months prior with documented imaging confirmation of resolution (for significant events) and investigator discretion.

12. Subjects with clinically significant platelet abnormalities or coagulopathy; adequate platelet counts and coagulation parameters must be confirmed, and any reversible coagulopathy corrected prior to dosing.
13. Subjects requiring full-dose anticoagulation or high-intensity antiplatelet therapy on high dose nonsteroidal anti-inflammatory drugs (NSAIDs) are excluded.
14. Diabetic patients with poor glycemic control, including but not limited to: a) 2 fasting blood glucose >10mmol/L, or b) concomitant diabetic gangrene.
15. Participants with poorly controlled hypertension by 2 kinds of antihypertensive drugs (systolic blood pressure>150 mmHg or diastolic blood pressure >100 mmHg).
16. Participants with stroke or transient ischemic attack (TIA) within 6 months before Screening.
17. Active autoimmune diseases and inflammatory diseases, such as systemic lupus erythematosus, psoriasis requiring systemic treatment, rheumatoid arthritis, inflammatory bowel disease and Hashimoto's thyroiditis, etc. Participants with skin diseases that do not require systemic treatment (such as vitiligo, psoriasis), well-controlled type 1 diabetes, or hypothyroidism are permitted. For autoimmune conditions that are active but stable and low-grade on systemic therapy, discussion with the medical monitor is required prior to Screening.

    Note: Active autoimmune or inflammatory disease is defined as disease within 6 months with clinically significant flare, new/progressive clinical signs, or objective inflammation requiring intervention or corticosteroid dose >10 mg prednisone equivalent daily. Stable disease on unchanged maintenance immunosuppression for ≥6 months, positive serology without clinical activity, or well-controlled endocrinopathies on hormone replacement alone do not constitute active disease.
18. Participants with advanced/clinically significant lung diseases, such as poorly controlled COPD and asthma, restrictive lung disease, pulmonary hypertension etc.

19. Participants who have a history of noninfectious interstitial lung disease (ILD)/pneumonitis that required treatment with steroids, have current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
20. Concurrent pulmonary disease resulting in severe impaired respiratory function, including but not limited to the following:
    - Any underlying pulmonary disease (eg, pulmonary embolism, severe asthma, severe COPD within 3 months prior to information)
    - Restrictive lung disease
    - Previous unilateral total lung resection
21. Participants with pulmonary hemorrhage risk: evidence on baseline chest imaging of pulmonary hemorrhage risk, including cavitary primary lung lesions, central tumors with major vessel encasement/invasion, or other imaging findings judged by the investigator to confer unacceptable risk of hemorrhage.
22. Participants with chest-pelvic effusion requiring drainage and/or symptomatic pleural-pelvic effusion, or pericardial effusion within 4 weeks prior to Screening.
23. Participants with primary tumors in the central nervous system (CNS), active or untreated CNS metastases or carcinomatous meningitis should be excluded. Participants with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks and have no evidence of new or enlarging brain metastases and no requirements for corticosteroids 14 days prior to Screening.

    Clinical CNS metastasis is defined as:
    - Seizure-free state lasting > 12 weeks with or without antiepileptic drugs
    - Stable imaging as evidenced by consecutive MRIs at least 4 weeks apart
24. Participant with active or untreated hemorrhagic CNS lesions.
25. Participants with pre-existing Grade ≥2 peripheral neuropathy.
26. Participants with a history of anaphylaxis or severe hypersensitivity reactions to:
    - recombinant humanized antibodies or human–mouse chimeric antibodies
    - any component of SI-B037
27. Previous organ transplantation or allogeneic hematopoietic stem cell transplantation.
28. Subjects with recent surgery, biopsy, or invasive procedures without adequate wound healing prior to study enrollment.
29. Participants with known or suspected human immunodeficiency virus (HIV) infection (HIV antibody positive).

Exceptions: Participants are allowed to participate if **all** the following criteria are met:

- undetectable HIV RNA and CD4 count ≥350 cells/µL at Screening
- no acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 12 months prior to Screening

  AND

- on stable antiretroviral therapy (ART) for at least 4 weeks prior to enrollment, with projected continuation of ART as clinically indicated while on the study

30. Participants with known active hepatitis B virus (HBV) infection (positive hepatitis B surface antigen [HBsAg] test). Exceptions: Participants with a chronic inactive HBV infection are eligible if all the following criteria are met:
    - HBV DNA viral load <500 IU/mL
    - normal AST and ALT, or if liver metastasis is present, AST and ALT <3 × ULN that are not attributed to HBV infection

      AND

    - on antiviral treatment as clinically indicated
31. Participants with known active hepatitis C virus (HCV) infection (HCV antibody positive and HCV-RNA > the lower limit of detection). Exception: Participants with a positive anti-HCV antibody are eligible only if quantitative polymerase chain reaction (qPCR) is negative for HCV-RNA.
32. Participants with active or latent tuberculosis.
33. Participants with active infections requiring IV antibiotic, antiviral, or antifungal treatment, such as severe pneumonia, bacteremia, sepsis, etc., within 1 week prior to first dose of study treatment. Participants on stable oral antimicrobials with no clinical or laboratory evidence of active infection are eligible.
34. Participated in another clinical trial within 4 weeks prior to first dose of study treatment.
35. Participants who are pregnant, breastfeeding, or planning to become pregnant during the study.
36. History of fistula, gastrointestinal perforation, or abdominal abscess within 6 months prior to the first dose.
37. Participant with moderate or major hemoptysis history.
38. Participant has tumors invading large blood vessels-Imaging examination shows that the tumor has:
    - tumor has invaded or wrapped the large blood vessels of the chest such as pulmonary artery, aorta, pulmonary vein, etc. (physician's discretion)

- tumor has invaded or wrapped pericardium and heart (physician's discretion)

39. Other conditions that the investigator or sponsor believes are not suitable for participating in this clinical trial.

5.3. Contraception

5.3.1. Definitions Related to Childbearing Potential

Individuals of childbearing potential (IOCBP) are defined as sexually active fertile participants and their partners.

Female participants are considered IOCBP unless one of the following criteria are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman >45 years old in the absence of other biological or physiological causes). In addition, females <55 years old must have a serum FSH level >40 mIU/mL to confirm menopause.

Highly effective methods of contraception are defined in Appendix 5.

5.3.2. Contraception Requirements

IOCBP must have a negative serum pregnancy test at Screening and must be nonlactating. IOCBPs must agree to use highly effective methods of contraception during the course of the study and for 4 months for men and 7 months for women after the last dose of study treatment. An additional contraceptive method, such as a barrier method (eg, condom), is recommended.

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

Not applicable. No restrictions are required.

5.4.2. Caffeine, Alcohol, and Tobacco

Not applicable. No restrictions are required.

5.4.3. Physical Activity Restrictions

Not applicable. No restrictions are required.

5.4.4. Other Activity Restrictions

Not applicable. No restrictions are required.

5.5. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the trial but do not meet the protocol-defined eligibility criteria (refer to Section 5.1 and Section 5.2 screening failure (eg, eligibility criteria not met, subject withdrew consent, other reasons), and any SAEs, or AEs

related to a trial assessment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened once. Rescreened subjects will be assigned a new subject ID. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised.

All eligibility criteria must be reassessed at the rescreening visit. The following screening assessments may be used for rescreening if performed <28 days prior to Cycle 1 Day 1 or if approved by the sponsor:

- CT and MRI scans with acquisition date <28 days prior to Cycle 1.
- Screening laboratory assessments with the protocol-defined timelines as indicated in Section 1.3 and Section 8
- Tumor biopsy sample.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and non-investigational medicinal products, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

Study intervention includes both IP and non-IP as indicated in Table 6.

6.1. Study Intervention(s) Administered

Table 6 SI-B037 Investigational Product

Drug Product Code:	**SI-B037**
INN	NA
Active Ingredient:	Anti-VEGF-A IgG1 backbone + C-terminal anti-PD-1 scFv via GS linker
Composition:	Anti-VEGF-A IgG1 backbone + C-terminal PD-1 scFv via GS linker
Dosage Form:	Injectable solution
Strength:	200 mg/per vial
Route of Administration:	Intravenous Infusion
Manufacturer:	Baili-Bio (Chengdu) Pharmaceutical Co., Ltd. No.139, Baili Road, Chengdu Cross-Strait science and technology park, Wenjiang District, Chengdu, Sichuan, China.

Abbreviations: GS=glycine-serine; IgG=immunoglobulin G; NA=not applicable; PD-1=programmed cell death protein 1; scFV=single-chain variable chain; VEGF-A= vascular endothelial growth factor A.

Table 7 Study Arm

Arm Title	**SI-B037**
Arm Type	Experimental
Arm Description	Participants will receive SI-B037 administered by IV
Associated Intervention Labels	SI-B037

6.2. Preparation, Handling, Storage, and Accountability

A sufficient quantity of the IP will be provided by the sponsor during the study. The study sites will handle the investigational drug as detailed below.

Information such as product name, strength, protocol number, storage conditions, vial number, batch number, manufacturing date, expired date, sponsor name, etc. shall be printed on the packages of the investigational drugs, with the notice “For intravenous infusion only. For investigational use only. Caution: New Drug—Limited by Federal (or United States) law to investigational use” indicated.

Upon receipt of the SI-B037 shipment, the pharmacist, or a designee, will conduct an inventory and return an acknowledgement that all SI-B037 was received refrigerated at 2 to 8°C and

undamaged, thereby maintaining the Good Manufacturing Practices status of the product during shipment.

The investigator, or approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss, or other disposition of SI-B037. The sponsor will supply drug accountability forms to be used in this study.

The sponsor or designee will arrange for the return of SI-B037 vials. The destruction procedure for used vials is to be decided locally to comply with local regulations and procedures.

Drug accountability will be reviewed by the monitor during routine monitoring visits. No vials of SI-B037 can be destroyed or returned until the study monitor has reconciled all vials of SI-B037.

Additional details are provided in the Pharmacy Manual and Investigator Brochure.

6.3. Assignment to Study Intervention

Not applicable, as this is an open-label study.

6.4. Blinding and Masking

Not applicable, as this is an open-label study.

6.5. Study Intervention Compliance

Refer to pharmacy manual

6.6. Dose Modification

After the first treatment cycle has been completed, management of adverse reactions may require a temporary dose delay, dose reduction, or treatment discontinuation of SI-B037 according to CTCAE v6.0 and as described in Table 8 and Table 9. A maximum of 2 dose reductions is permitted for recurrent Grade 3 or higher toxicities as specified in Table 8 and Table 9. Further guidance on the management of toxicities related to SI-B037 treatment is provided in Appendix 8.

Note: re-escalation is not allowed after a subject's dose is reduced, and dose adjustments are not allowed during the DLT observation period.

Table 8 Dose Reductions

First dose reduction	Second dose reduction
Reduce by 20% of initial dose	Reduce by 40% of initial dose

Notes:

a. Re-escalation is not allowed after a subject's dose is reduced, and dose adjustments are not allowed during the DLT observation period.

b. A maximum of 2 dose reductions will be allowed.

Table 9 Dose Delays, Reductions and Treatment Discontinuations

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Hematologic Toxicity: Rule out non-immune related causes prior to assessing attribution to drug (i.e. infection, concomitant medication, etc.).				
Neutropenia	Grade 3 (ANC < 500-100/mm^3) or <0.5×10^9/L)	Withhold until recovery to ≤ Grade 2, then may reduce by one dose level per PI discretion. For a recurrent Grade 3 event, mandatory dose reduction or permanent discontinuation if already dose reduced.	Rule out any associated infection, Consider prophylactic growth factor	Monitor for signs of infection
	Grade 4 (<100/mm^3 or <0.1 x 10^9/L)	Withhold until recovery to ≤ Grade 2, then reduce by one dose level (Table 8). For a recurrent ≥3 event, permanent discontinuation.	Provide urgent supportive treatment and evaluate for infection, immune-mediated agranulocytosis, marrow failure, and other causes.	Treat per institutional guidelines
Febrile Neutropenia	Grade 3	Withhold until improvement and reduce the dose (Table 8).	Urgent intervention is required	Initiate prompt infectious evaluation and empiric antimicrobial treatment. Growth factor support may be administered as clinically indicated.
	Grade 4	Permanently discontinue		
Anemia	Grade 3	Withhold until recovery to Grade ≤2 and maintain current dose.	Treat according to institutional guidelines	Assess if the event is immune-mediated, recommend hematology consult
	Grade 4	Withhold until recovery to Grade ≤2. May reduce the dose by 1 level if event is not immune-mediated (Table 8). Otherwise permanent discontinuation.	Treat according to institutional guidelines with urgent intervention and clinical stabilization	Assess if the event is immune-mediated, recommend hematology consult
Thrombocytopenia	Grade 2 (<75,000 - 50,000/mm^3 or	Withhold until recovery to Grade ≤1 and then resume at current dose. If Grade 2 is recurrent, prolonged (> 2 weeks), or clinically significant, reduce by 1 dose level (Table 8).	Treat according to institutional guidelines	Monitor for bleeding and review concomitant anticoagulation and antiplatelet therapy

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
	<75.0 - 50.0 x 10^9/L)			
	Grade ≥3	**Grade 3** (<50,000 - 10,000/mm^3 or <50.0 - 10.0 x 10^9/L)**:** Withhold until recovery to Grade ≤1. Resume the dose at one dose reduction (Table 8) only if the event is determined not to be immune-mediated and there is no clinically significant bleeding; otherwise permanently discontinue **Grade 4** (<10,000/mm^3 or <10.0 x 10^9/L)**:** permanently discontinue	Treat according to institutional guidelines	Evaluate for immune thrombocytopenia, DIC, thrombotic microangiopathy, marrow involvement, and other causalities
Pulmonary disorders				
Clinically significant hemoptysis in patients with pulmonary lesions (eg, bright-red blood in sputum, ≥"teaspoon" volume, or raising concern for pulmonary hemorrhage)	Any Grade	Permanently discontinue	Evaluate and treat source as per local practice	
Pneumonitis/ILD	Grade 2	Withhold for 4 weeks and resume same dose if it resolves within 4 weeks	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Hepatic Disorders				

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
AST / ALT elevation	Grade 1 or 2	Withhold dose until AST/ALT recovers to Grade ≤1 or baseline. Resume at the same dose level. For recurrent Grade 2 events requiring treatment interruption, consider dose reduction by one dose level (Table 8) at investigator/sponsor discretion.	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue[1]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Increased bilirubin	Grade 1 and 2	**Grade 1:** Continue dose with close monitoring. If bilirubin continues to increase or persists for >2 weeks, withhold SI-B037 until recovery to baseline or Grade ≤1, then resume at the same dose level. **Grade 2:** Withhold dose until recovery to baseline or Grade ≤1. Resume at the same dose level. For recurrent Grade 2 bilirubin elevations requiring treatment interruption, consider dose reduction by one dose level (Table 8).	Evaluate and treat source as per local practice	
	Grade 3 and 4	Permanently discontinue	Treat per local SoC	
Endocrine Disorders				
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold until clinically stable and then resume at the same dose. Hyperglycemia Grade 3-4, reduce by 1 dose (Table 8).	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Hypophysitis	Grade 1 and 2	Withhold; resume if endocrinopathy improves to be asymptomatic or is adequately controlled with only physiological hormone replacement, resume at same dose. For recurrent Grade 2 events requiring treatment interruption, consider dose reduction by one dose level (Table 8).	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) Consider pituitary scan
	Grade 3 that is also associated with corresponding abnormal lab and/or pituitary scan	Withhold SI-B037 until symptoms improve to Grade ≤1 or baseline and the patient is clinically stable on hormone replacement therapy and/or corticosteroids, as indicated. Resume at one dose level reduction (Table 8). For recurrent Grade 3 hypophysitis, permanently discontinue SI-B037.		
	Grade 4	Withhold or permanently discontinue[1] Mandatory discussion with and approval from medical monitor needed prior to resuming therapy		
Hyperthyroidism	Grade 2	Continue treatment with appropriate medical management.	Treat with non-selective beta blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold dose until resolution to Grade ≤1 and clinical stabilization. Resume at the current dose level or permanently discontinue[1]		
Hypothyroidism	Grade 2	Continue dose and initiate or optimize thyroid hormone replacement therapy as clinically indicated. If treatment is interrupted, resume at the same dose level once symptoms improve to Grade ≤1 and the patient is clinically stable.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
	Grade 3	Withhold until symptoms improve to Grade ≤1 or baseline and appropriate thyroid hormone replacement therapy has been initiated. Resume at the current dose level when clinically stable.		
	Grade 4	Withhold until resolution to Grade ≤1 or baseline and clinically stable on thyroid hormone replacement therapy. Resume at the current dose level.		
Cardiac Disorders				
Congestive Heart Failure	All Grades	Permanently discontinue	Treat as per local SoC	
Myocarditis	Grade 1	Withhold until cleared by a cardiologist; resume same dose level	Based on severity of AE administer corticosteroids	
	Grade 2, 3, or 4	Permanently discontinue		
Hypertension (new or worsening)	Grade ≤2	Maintain dosing	Monitor BP and treat per local SoC	
	Grade 3	Withhold until improvement to Grade ≤ 1. Reduce the dose (Table 8)	Treat as per local SoC. If there is a significant difference between the BP readings (>20/10 mmHg) from prior visit, blood pressure should be repeated to confirm result.	
	Grade 4	Permanently discontinue	If BP does not resolve to within the target reading after treatment with more than 3 antihypertensive drugs, or if the study participant has multiple	

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
			drug intolerance refer to hypertension specialist. If systolic BP ≥220 mmHg, evaluate for organ function deterioration to confirm or exclude hypertensive crisis and treat per local SoC. In the case of malignant hypertension, hypertensive crisis, or hypertensive encephalopathy with organ function decompensation treat as per local SoC.	
Renal Disorders				
Nephritis and Renal dysfunction	Grade 2	Withhold dose until serum creatinine returns to Grade ≤1 or baseline and renal function is clinically stable. Resume dose at the same dose level. For recurrent Grade 2 nephritis/renal dysfunction requiring treatment interruption, reduce by one dose level (Table 8).	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Serum Creatinine Increased	Grade 2 or 3	Withhold until improvement to Grade ≤ 1 or baseline. Reduce the dose (Table 8).	Monitor creatinine every 2-3 days. Initiate 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent. If improves to Grade ≤1, taper steroids over at least 1 month.	Consider prophylactic antibiotics for opportunistic infection Consider renal biopsy with nephrology consult

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
			If elevation persists > 7 days or worsens, treat as Grade 4.	
	Grade 4	Permanently discontinue	Monitor creatinine daily. Initiate 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent. If resolves to Grade ≤1, taper steroids over at least 1 month and add antibiotics for opportunistic infections. If no improvement or worsening, add additional immunosuppression.	Consult nephrologist Consider renal biopsy
Proteinuria	Grade 2	Withhold dose until improves to Grade ≤1 (<2 g/24 hr or UPCR <2000 mg/g). Resume dose at the same dose level. For recurrent Grade 2 proteinuria requiring treatment interruption, reduce by one dose level (Table 8).	Treat as per local SoC. 2+ or greater on dipstick should undergo further assessment with 24-h urine collection. Assessment of UPCR is an acceptable alternative to 24-h urine collection; UPCR should be < 2000 mg/g to resume treatment.	
	Grade 3 or 4	Permanently discontinue	Treat as per local SoC	

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Adrenal insufficiency	Grade 2	Withhold dose until symptoms improve to Grade ≤1 or baseline and appropriate corticosteroid replacement therapy has been initiated. Resume at the same dose level once the patient is clinically stable on hormone replacement therapy. For recurrent Grade 2 events requiring treatment interruption, reduce by one dose level (Table 8).	Treat as per local SoC. If symptomatic with abnormal lab/pituitary scan: 1-2 mg/kg/day methylprednisolone IV or po equivalent. If improves (with or without hormone replacement therapy, taper steroids over at least 1 month). Consider prophylactic antibiotics for opportunistic infections. Initiate appropriate hormone therapy.	Evaluate endocrine function and consider consultation with endocrinology
	Grade 3 or 4 or adrenal crisis	Withhold until improvement to Grade ≤ 1 or permanently discontinue[1] Mandatory discussion with and approval from the medical monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.	Rule out sepsis. Stress-dose of IV steroids with mineralocorticoid activity. IV fluids	Consult endocrinologist
Gastrointestinal Disorders				
Upper gastrointestinal bleeding	Grade 1 and 2	The infusion should be stopped and intervention initiated. Withhold until recovery to Grade ≤1. If resolved: ≤7 days after medical treatment, maintain current dose. If resolved >7 days from date of onset, reduce the dose by 1 level (Table 8).	Treat per local SoC	
	Grade 3 and 4	Permanently discontinue	Emergency intervention is required to administer	

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
			transfusion; invasive intervention indicated; hospitalization.	
Diarrhea / Colitis	Grade 2 or 3	Withhold until resolved to ≤ Grade 1[2] Reduce the dose (Table 8)	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie,peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue	Treat per local SoC	
Pancreatitis	Grade 3-4	Permanently discontinue	Treat as per local SoC	
Neurological Disorders				

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Guillain-Barre Syndrome (GBS) Myasthenia Gravis (MG) Posterior reversible encephalopathy syndrome Encephalopathy Posterior reversible encephalopathy syndrome Myelitis	All Grades	Permanently discontinue	Treat symptoms as per local SoC. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or PO equivalent. If improves, taper steroids for at least 1 month. If it worsens or atypical presentations, consider intravenous immunoglobulin or other immunosuppressive therapies per local guidelines.	Consider neurology consult. Add prophylactic antibiotics for opportunistic infections.
Other Neurologic Event	Grade 2	Withhold until resolution to baseline. Resume at the same dose level	Treat as per local SoC. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or PO equivalent. If event improves, taper steroids over a period of at least 1 month.	Consider neurology consult
	Grade 3 or 4	Permanently discontinue	Treat symptoms per local guidelines: 1-2 mg/kg/day methylprednisolone IV or IV equivalent.	Obtain neurology consult. Add prophylactic antibiotics for opportunistic infections.

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
			If improves to Grade 2, taper steroids over a period of at least 1 month.	
Skin Disorders				
Rash/Skin Toxicities	Grade 1 or 2	Continue dose with appropriate supportive treatment. If rash persists for >1 week or worsens despite optimal management, withhold dose until improvement to Grade ≤1 or baseline. Resume dose at the same dose level upon recovery. For recurrent Grade 2 rash requiring treatment interruption, reduce by one dose level (Table 8).	Symptomatic therapy (eg, antihistamines, topical steroids) if persists >1 week, consider skin biopsy. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or PO equivalent. Once improving, taper steroids over at least 1 month.	Consider prophylactic antibiotics for opportunistic infection
	Grade 3	Withhold until rash reduces to ≤ 10% body surface area. Reduce the dose (Table 8).	Consider skin biopsy 1-2 mg/kg/day methylprednisolone IV or PO equivalent. If improves to Grade 1, taper steroids over at least 1 month.	Consider dermatology consult
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Withhold until SJS, TEN or DRESS is ruled out and rash reduces to ≤ 10% body surface area. Reduce the dose (Table 8).	Treat as per local SoC	Referral for specialized care to assessment and treatment
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	Treat as per local SoC	Referral for specialized care to assessment and treatment
Vascular Disorders				

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Arterial thromboembolism	Grade 3 or 4	Permanently discontinue	Treat per local SoC	
Venous thromboembolism	Grade 3	Withhold dose for ≥2 weeks during full-dose anticoagulation. Resume dose only when anticoagulant therapy is stable (e.g., LMWH or equivalent), no Grade 3 or 4 hemorrhagic events have occurred during anticoagulation, and the patient is clinically stable. Resume at one dose level reduction (Table 8).	Treat per local SoC	
	Grade 4	Permanently discontinue	Treat per local SoC	
Other Disorders				
Hemorrhage	Grade 1-2 including pulmonary hemorrhage	Maintain dosing if the participant is hemodynamically stable. Consider withholding, if clinically indicated. Resume at the same dose level. For recurrent Grade 2 hemorrhage requiring treatment interruption, reduce by one dose level (Table 8).	Treat per local SoC	
	Grade 3 or 4	Permanently discontinue	Treat per local SoC	
Bleeding: Mucosal (epistaxis, hematuria, hemoptysis, gingival bleeding, self-limited vaginal spotting)	Grade 1 or 2	Withhold and evaluate the source, if resolved within 7 days continue at the same dose	Treat per local SoC	
	Grade 3 or 4	Withhold and consider permanent discontinuation depending on severity[1] If drug continued, Reduce the dose (Table 8).		
	Grade 1 or 2	Permanently discontinue	Treat per local SoC	

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Bleeding: Nonmucosal (GI, CNS, Internal)	Grade 3 or 4	Permanently discontinue	Immediate intervention is required	
Myositis	Grade 2	Withhold dose until myositis improves to Grade ≤1 or baseline and the patient has completed appropriate medical management, including corticosteroids if indicated. Resume dose when clinically stable, per protocol. For recurrent Grade 2 myositis requiring treatment interruption, manage per protocol dose modification guidelines; dose reduction (Table 8) or permanent discontinuation may be considered [1]	Rule out non-inflammatory causes. Check creatine kinase. If mild pain - monitor creatine kinase. If moderate/severe or life-threatening - 1.0-2.0 mg/kg/day methylprednisolone or equivalent. Consider muscle biopsy. If improves taper steroids over at least 1 month. Treat as per local SoC.	Monitor creatine kinase until symptoms resolved or steroids discontinued
	Grade 3 or 4	Permanently discontinue		
Perforations/Fistula	Grade 3 or 4	Permanently discontinue	Treat as per local SoC	
Surgical and wound healing complications	Wound healing complications	Withhold dose until complete wound healing has occurred and the participant is clinically stable. Resume dose at the same dose level upon recovery. For recurrent wound healing complications requiring treatment interruption, reduce by one dose level (Table 8).	Treat per local SoC	
	Surgery during the trial	Withhold for at least 21 days before elective surgery and for at least 21 days after surgery until complete wound healing has occurred. Resume at the		

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
		same dose level once adequately healed.		
	Wound dehiscence and/or wound healing complications that require medical intervention	Permanently discontinue		
Uveitis	Grade 3	Withhold dose. Initiate systemic high-dose corticosteroids: e.g., prednisone 1–2 mg/kg/day or IV methylprednisolone 1–2 mg/kg/day, plus intensive ophthalmology management (topical/intravitreal steroids as indicated). Permanently discontinue study drug for confirmed or suspected immune-mediated Grade 3 uveitis, particularly if: posterior or panuveitis, vision-threatening, or refractory or recurrent despite steroids.	Referral to ophthalmologist is required. Dosing may resume if uveitis responds to topical therapy (eye drops). If oral steroids are required, then permanently discontinue study drug.	
	Grade 4	Permanently discontinue		
Other Immune Related AEs				
All other immune related AEs	Intolerable/persistent Grade 2	Withhold dose until the event improves to Grade ≤1 or baseline. Resume at the same dose level upon recovery. For recurrent Grade 2 events requiring treatment interruption, reduce by one dose level (Table 8).	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold dose until recovery to Grade ≤ 1 or baseline, then resume treatment or reduce the dose 1 level (Table 8) based on the investigator or treating physician's assessment.		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
Non-laboratory AEs				
All other non-laboratory related AEs	Grade 3	Withhold dose until recovery to Grade ≤ 1 or baseline, then resume treatment or reduce the dose 1 level (Table 8) based on the investigator or treating physician's assessment.	Provide appropriate medical management, supportive care, and specialty consultation as indicated; consider hospitalization if clinically warranted.	Monitor until resolution or stabilization; perform additional evaluations and follow-up as clinically indicated, and document outcome, recurrence, and any concomitant treatment.
	Grade 4	Permanently discontinue		
Infusion Reaction				
Infusion-Related Reactions	Grade 1	No effect on Infusion	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Premedication of Subsequent Dosing: none	
	Grade 2	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).	

Toxicity	Toxicity Grade	Action taken to SI-B037	Recommended AE Management	Monitor and follow-up
	Grade 3 and 4	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Premedication at Subsequent Dosing No subsequent dosing. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing	

1. Withhold or permanently discontinue SI-B037 is at the discretion of the investigator or treating physician.

2. If drug is withheld due to toxicity for more than 6 weeks consult the sponsor and medical monitor.

Dose reduction may be considered for selected clinically significant Grade 2 adverse events that are persistent, recurrent, intolerable to the participant, or require prolonged medical management despite optimal supportive care, following discussion with the sponsor and medical monitor.

NOTE: For participants with Grade 3 or 4 immune related endocrinopathy where withhold of SI-B037 is required, SI-B037 may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

6.7. Continued Access to Study Intervention After the End of the Study

There is currently no plan to provide access to the interventional trial product to participants following the end of the trial.

6.8. Treatment of Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses may meet the regulatory definition of an AE or SAE and should be properly reported.

For this study, any dose of SI-B037 that is 10% higher than the highest dose will be considered an overdose.

There is no known antidote for treating an overdose of SI-B037. The sponsor does not have specific recommendations for the treatment for an overdose.

In the event of an overdose, the investigator should:

Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.

Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and Concomitant Therapy

Enrolled participants will inform the study investigator about all prior and concomitant medications or vaccines administered from the Screening visit to study termination (including the indication, dose, frequency, start and end date, and time of administration). All concomitant treatments and combined medications received by the subject from the time of Screening to 30 days after the last dose will be recorded in the eCRF with the following information:

- International non-proprietary name
- Reason for use (indication)
- Dates of administration, including start and end dates as applicable
- Dosage information (dose and frequency)

If a related SAE is reported 30 to 60 days after the last dose, all concomitant medications related to the SAE should be recorded in the SAE report.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and supplements.

The combined use of antitumor therapy, including chemotherapy, biological therapy, immunotherapy, radical radiotherapy (with the exception of palliative use only if radiographic disease progression has been ruled out), targeted therapy, herbal or holistic medicines with antitumor indications and other investigational drugs as described in the exclusion criteria (Section 5.2) are prohibited during the study period. In addition, concomitant medications that prolong the QT/QTc interval are prohibited (Cardiovascular Medicine 2026).

Study participants with bone disease may receive bisphosphonates during the study if tolerated.

Use of preventive medications for IRRs, nausea and vomiting are described in Section 6.9

All medication taken by the participant for a concurrent medical condition is permitted and must be recorded on the CRF.

6.9.1. Drugs That May Interact with SI-B037

During this study, concurrent use of antitumor treatments (including chemotherapy, immunotherapy, radiotherapy, bioreactive modifiers, traditional Chinese medicines with antitumor indications, etc.) or other investigational drugs is prohibited. Palliative radiotherapy to relieve bone pain is permitted during the study. Concomitant medications associated with increased bleeding risk, including therapeutic anticoagulants or NSAIDs, should be restricted or closely managed per protocol.

Agents that may impair wound healing or increase hemorrhagic risk should be avoided around dosing and procedures.

6.9.2. Preventive Medications

Primary prevention is allowed for IRRs, diarrhea, nausea, and vomiting.

Infusion-Related Reactions: Premedication for prevention of IRRs with antipyretics and H1 and H2 blockers should be administered before each infusion. Corticosteroids (hydrocortisone 50 mg or equivalent PO or IV) may be administered prior to subsequent infusions if the participant had experienced an IRR with a previous infusion. Additional details of recommended treatment of IRRs are described in Section 6.9.3.1

Diarrhea, Nausea and Vomiting: Premedication with a 2-drug antiemetic regimen is recommended after the first cycle if needed. If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg orally [PO] or IV). Anticipatory nausea can be treated with olanzapine. Prevention of diarrhea should follow institutional guidance.

6.9.3. Management of SI-B037 Toxicities

The NCI-CTCAE v6.0 is used to grade the severity of AEs (Appendix 3). Any AEs that are not included under the CTCAE v6.0 will be graded for severity following the guidelines in Appendix 4. The guidelines for management of toxicities that may be associated with SI-B037 are based on the assessment of severity according to these criteria. Toxicities should be managed in accordance with standard medical practice and treatment guidelines. All clinically appropriate

imaging or laboratory testing should be used to fully assess toxicity to determine the appropriate treatment. Appropriate follow-up studies should be used to follow all toxicities to resolution. Additional monitoring may be required in those participants. Instructions for dose delays, reductions, or discontinuations for treatment-related toxicities are provided in Section 6.6, Table 8 and Table 9.

6.9.3.1. Infusion-Related Reactions

Infusion-related reactions (IRRs) are defined as symptoms that occur during and within the first 6 hours after infusion. Symptoms can include fever, chills, rigors, arthralgias, myalgias, urticaria, pruritus, rash, diaphoresis, hypotension, dizziness, syncope, hypertension, dyspnea, cough, and wheezing, as well as severe hypersensitivity reactions including anaphylactic reactions. IRRs should be treated in accordance with best clinical practices and standard institutional guidelines. Because of the potential for life-threatening IRRs, SI-B037 should only be administered in a setting in which appropriately trained medical staff, emergency equipment and medications are available if resuscitation is required. NCI-CTCAE v6.0 is used to grade the severity of all infusion-related AEs. Premedication for the prevention of IRRs is described in Section 8.5.7.

Grade 3 and Grade 4 Events

Grade 3 and Grade 4 IRR can include severe or clinically significant cardiopulmonary events and severe allergic reactions such as symptomatic bronchospasm and anaphylactic reactions. Grade 3 IRRs are defined as those which are prolonged and do not improve with symptomatic treatment and/or brief interruption of treatment, reactions that recur following treatment, and reactions that require hospitalization. Grade 4 reactions include potentially life-threatening reactions and require urgent intervention. Severe allergic and anaphylactic reactions should be treated in accordance with best clinical practices and standard institutional guidelines. If Grade 3 or Grade 4 IRRs occur, SI-B037 should be permanently discontinued.

Grade 2 Events

Grade 2 IRRs are defined as those that require infusion interruption and respond to symptomatic treatment; prophylactic medications are indicated for ≤24 hours. For Grade 2 IRRs, the infusion should be interrupted for at least 15 minutes until symptoms are resolved. After symptoms resolve, the infusion should be resumed at a slower infusion rate. For recurrent Grade 2 infusion reactions that fail to recover within 6 hours, despite optimal management, permanently discontinue.

6.9.3.2. Pulmonary Toxicities

Pulmonary toxicity can manifest as worsening lung function, characterized by symptoms such as shortness of breath, fever, cough, and difficulty breathing. In such cases, the investigator should conduct a thorough evaluation including blood tests, inflammatory markers assessment, erythrocyte sedimentation rate analysis, and chest CT examination (high-resolution CT [HRCT] is recommended if possible) once the subject's vital signs stabilize. If necessary, bacterial cultures (sputum or blood) should be obtained to diagnose potential infectious pneumonia. If infectious pneumonia is confirmed, the investigator will initiate anti-inflammatory treatment based on the subject's condition and bacteriological examination results.

Interstitial Lung Disease and Pneumonitis

To mitigate the risk of ILD/Pneumonitis, it is recommended to:

- Conduct a comprehensive assessment of individual risk factors.
- Perform baseline evaluations including respiratory function tests, physical examination, and chest imaging.
- Implement standardized diagnosis and treatment protocols.
- Establish a multidisciplinary expert network to facilitate prompt consultation.
- Engage in open communication with subjects to educate them about the clinical manifestations of ILD/Pneumonitis and associated risks, enabling early detection and consultation for new symptoms.

6.9.3.3. Cardiotoxicities

Investigators may increase the frequency or scope of cardiac monitoring, as clinically indicated, including the use of echocardiography to assess changes in left ventricular ejection fraction and end-diastolic volume. Any ECG abnormalities identified during Screening or at baseline that are deemed clinically significant by the investigator should be documented and reported as comorbid conditions.

During treatment, suspected or confirmed cardiotoxicity will be managed through interruption, discontinuation, or dose modification in accordance with Section 6.6, Table 8 and Table 9.

6.9.3.4. Gastrointestinal Toxicities

Nausea, vomiting, and diarrhea may be SI-B037 associated toxicities. Appropriate treatment, including fluid and electrolyte replacement, is required as needed to minimize the risk of serious consequences such as dehydration.

Instructions for dose reduction for treatment-related gastrointestinal toxicities are provided in Section 6.6, Table 8 and Table 9.

Nausea and Vomiting

Instructions for the use of pre-medications for prophylactic treatment of nausea and vomiting and anticipatory nausea are provided in Section 6.9.3. Do not hold the dose for Grade 3 nausea unless Grade 3 nausea persists despite maximal optimal medical management. Subjects should be treated for delayed nausea and vomiting on Days 2 and 3 with 5-HT3 receptor antagonist (ondansetron or palonosetron) monotherapy and other agents if needed. Steroids may be added if symptoms do not resolve with these other agents. Consider olanzapine for persistent or anticipatory nausea; an olanzapine dose of 2.5 mg or 5 mg at bedtime is recommended. NK1 receptor antagonists (fosaprepitant and aprepitant) may be administered.

Diarrhea

Dietary modification should be recommended for the management of diarrhea, including a bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration, and discontinuation of lactose-containing foods and drinks and alcohol. Loperamide should be administered at the onset of treatment-related Grade 1 or Grade 2 diarrhea, at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If

diarrhea is not resolved after 24 hours, add diphenoxylate/atropine and/ or opium tincture as clinically indicated.

Add octreotide 100 to 150 µg subcutaneously (SC) 3 times per day (TID) if diarrhea persists. For Grade 3 or Grade 4 diarrhea, consider hospitalization, and treat with IV fluids, and octreotide. Antibiotics can be administered as clinically indicated.

If associated with neutropenia Grade ≤2, neutrophil changes should be dynamically monitored. If neutropenia is Grade ≥3, active G-CSF and empiric antibiotics should be given and if necessary, immunoglobulin should be used to combat infection.

Subjects who exhibit an excessive cholinergic response to SI-B037 (eg, abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (eg, atropine) for subsequent treatments.

Mucositis / Stomatitis

The management of mucositis should focus on prophylaxis and symptomatic relief. The following structured approach is recommended:

Prophylactic Measures:

- Subjects should be encouraged to chew on ice chips before and during chemotherapy infusion to help reduce the severity of mucositis by constricting blood vessels in the oral mucosa
- An emphasis should be placed on regular brushing and flossing, along with rinsing the mouth with saline solution or prescribed mouthwash, to prevent bacterial buildup and reduce the risk of infection
- An oral solution of dexamethasone 0.1 mg/mL to be used 4 times a day should be prescribed
- Subjects should be instructed to swish their mouthwash for 1 to 2 minutes and then expectorating the mouthwash. Local alternatives based on institutional or local guidelines may be used

Symptomatic Relief

- Encourage subjects to use steroid-containing mouthwash (eg, dexamethasone) more than 4 times a day for pain management and to reduce inflammation
- Consider using non-alcoholic and/or bicarbonate-containing mouthwash 4 to 6 times a day and doxepin 0.5 %, or use viscous lidocaine 2 % for additional pain relief
- Prescribe oral nystatin suspension or other topical antifungal agents to be used at least 15 minutes after the steroid-containing mouthwash, as recommended by institutional or local guidelines

Other Symptomatic Treatments:

- In severe cases, consider using clobetasol gel, magic mouthwash (a mixture of sucralfate, suspension of aluminum hydroxide, and diphenhydramine), or viscous lidocaine 2% for additional symptomatic relief. resuscitation, if necessary, followed

by endoscopy for diagnosis and treatment. Initial management of upper gastrointestinal bleeding should follow the American College of Gastroenterology (ACG) guideline as summarized in (Laine et al. 2021).

6.9.3.5. Hematological Toxicities

Neutropenia

Complete blood counts must be obtained and assessed locally prior to each infusion. The study drug should **only** be administered if ANC meets the following criteria:

- Cycle 1 Day 1: ANC ≥1500/mm3
- Subsequent cycles, Day 1: ANC >1000/mm3

Prophylactic use of growth factors should comply with American Society of Clinical Oncology guidelines (Smith et al. 2015).

Febrile Neutropenia

Neutropenia poses significant challenges in cancer treatment due to its potential to compromise treatment delivery and increase the risk of serious complications, such as febrile neutropenia (FN). The severity and duration of neutropenia directly correlate with the risk of infection, including potentially life-threatening bacterial, fungal, or viral infections. FN, characterized by fever in the setting of neutropenia, is particularly concerning as it can lead to treatment delays, dose reductions, and interruptions, ultimately undermining the effectiveness of chemotherapy regimens. Given the critical impact of neutropenia on treatment outcomes, its prevention and management are paramount in optimizing chemotherapy efficacy and patient safety. Prophylactic measures, such as the use of G-CSFs, can help mitigate the risk of neutropenia-related complications by stimulating neutrophil production and reducing the severity and duration of neutropenia. Additionally, close monitoring of blood counts, timely administration of supportive care measures, and prompt initiation of antibiotic therapy in the event of FN are essential components of comprehensive neutropenia management strategies.

Anemia

The treatment methods for associated anemia primarily encompass blood transfusion therapy, EPO administration, and iron supplementation and should follow local/institutional guidance; however, if no local guidance is available, the strategy below is recommended.

Blood transfusion, either with red blood cells or whole blood, is the primary clinical approach for managing anemia. This method offers the advantage of rapidly increasing hemoglobin concentration. The application of blood transfusion therapy can be categorized into the following groups:

Asymptomatic and without obvious complications

- During this phase, observation and regular reevaluation are suitable. For chronic anemia with stable hemodynamics, the transfusion target is to achieve a Hb level greater than 7.0 g/dL.

High-risk

- In cases where participants have received intensified chemotherapy or radiation therapy, or in the presence of comorbidities (such as heart disease, chronic lung disease, and cerebrovascular disease), blood transfusion may be considered. The goal of blood transfusion is to maintain Hb levels based on preventive symptoms and individual needs.

The initiation of erythropoietin (EPO) treatment is recommended when the Hb level is ≤10.0 g/dL. The target Hb value for EPO treatment is 12.0 g/dL. If the Hb level exceeds 12.0 g/dL, the dosage of EPO should be reduced or discontinued based on the individual participant's condition. The recommended medication plan includes administering 80,000 U once every 2 weeks or 120,000 U IV drip once every 3 weeks.

Continuous use of EPO in participants with renal failure caused by tumors or chemotherapy can lead to functional iron deficiency (ferritin ≤500 µg/L and transferrin saturation <50%). For participants with absolute iron deficiency (ferritin ≤30 µg/L and transferrin saturation <20%), iron supplementation treatment is necessary. Oral and parenteral iron supplementation are the main methods of iron supplementation. Common oral iron preparations include ferrous sulfate, ferrous fumarate, ferrous gluconate, and ferrous succinate, with ferrous sulfate being relatively commonly used in clinical practice. The iron content of different iron agents varies, and the oral dose is calculated based on 4 to 6 mg of elemental iron per kilogram of body weight per day. It is not recommended to exceed 1.5 to 2 mg per kilogram of body weight per dose. Equivalent to ferrous sulfate, this is approximately 30 mg per kilogram of body weight per day.

Vitamin C can enhance the absorption of oral iron, while phosphate can affect the absorption of iron. For participants who are intolerant to oral iron supplements or who have a weak response to iron supplementation therapy, it is recommended to use an extraintestinal route to supplement iron.

The management guidelines for anemia are summarized by Hb level in Table 10.

Table 10 Guidelines for the Management of Anemia

Hemoglobin (Hb) level	Treatment Strategy
8.0 g/dL ≤ Hb <10.0 g/dL	• Simultaneously use EPO with study treatment, with a target upper limit of 12.0 g/dL
6.0 g/dL ≤ Hb <8.0 g/dL	• Asymptomatic, no obvious cardiovascular complications: Delayed administration, use EPO until Hb recovers to ≥8.0 g/dL before administration • Asymptomatic but with comorbidities (heart disease, chronic lung disease, cerebrovascular disease) or high-risk (recent high-intensity chemotherapy or radiotherapy with rapid decrease in Hb): Delayed administration, blood transfusion, until it recovers to ≥8.0 g/dL before administration • Symptomatic (persistent tachycardia, shortness of breath, chest pain, motor dyspnea, mild headache, syncope, severe fatigue affecting work and habitual activities): Delayed administration, blood transfusion, until it recovers to ≥8.0 g/dL before administration
Hb <6.0 g/dL	• Delayed administration, blood transfusion until recovery to ≥8.0 g/dL before administration

Abbreviations: EPO=erythropoietin; Hb=hemoglobin.

Thrombocytopenia

Complete blood counts must be obtained and assessed prior to each infusion.

Thrombocytopenia is a potential adverse event associated with anticancer therapies, including agents targeting the VEGF pathway, and may increase the risk of bleeding in patients with cancer. Preventive measures and treatment strategies are essential for managing thrombocytopenia effectively. In participants suffering from severe chemotherapy-induced thrombocytopenia, the general goal is to prevent bleeding.

Vitamin K can be used to correct blood coagulation for participants taking warfarin or those lacking vitamin K-dependent coagulation factors (Factors II, VII, IX, and X). Vitamin K can be taken orally or injected SC or IV.

Platelet (PLT) transfusion is the only acute treatment method available for severe thrombocytopenia. If the participant is bleeding, or if PLT counts $<10 \times 10^9$/L (or $<20 \times 10^9$/L in case of fever), platelet transfusion is required to prevent massive bleeding. It is very important that hematopoietic growth factor used to promote platelet recovery be applied.

- Follow local/institutional guidance; however, if no local guidance for prevention is available, follow the guidelines for the treatment of thrombocytopenia provided in Table 11.

Table 11 Symptomatic Treatment for Thrombocytopenia

Grouping	Stratification	Recommendation
CIT with bleeding	Not applicable	Platelet transfusion or platelet transfusion + rhTPO or rhIL-11 or TPO-RA
CIT without bleeding	10×10^9/L < PLT count <100×10^9/L	rhTPO or rhIL-11 or TPO-RA
	PLT count ≤ 10×10^9/L	Platelet transfusion or platelet transfusion + rhTPO or rhIL-11 or TPO-RA

Abbreviations: CIT=chemotherapy-induced thrombocytopenia; PLT=platelet; rhIL-11=recombinant human IL-11; rhTPO=recombinant human thrombopoietin; TPO-RA=thrombopoietin receptor agonist.

RhTPO (Recombinant Human Thrombopoietin)

- Dose: 300 U/kg, once daily, administered continuously.
- Monitoring: Blood routine should be monitored during use, typically twice a week. For special cases, monitoring can be adjusted to once every other day as needed until the withdrawal standard is reached.

RhIL-11 (Recombinant Human Interleukin-11)

- Recommended Dosage: 25 to 50 μg/kg, administered via SC injection once daily, continuously for 7 to 10 days until the withdrawal standard is reached.

TPO-RA (Thrombopoietin Receptor Agonists) Avatrombopag:

- Initial Dose: 20 mg/day, taken orally once daily with food.
- Maximum Dose: 40 mg/day, taken orally once daily.
- Discontinue avatrombopag if, after taking 40 mg/day for 4 weeks, the platelet count remains below 50 × 109/L, or if taking 20 mg QW maintains the platelet count above 400 × 109/L.
- Adjust dose based on the investigator's assessment.

Romiplostim:

- Initial Dose: 1 mcg/kg, injected SC QW.
- Dose adjustment every 2 weeks based on platelet count until the minimum dose to maintain platelet response is reached.
- Maximum Daily Dose: Should not exceed 10 mcg/kg. Until the participant reaches 50 × 109/L or greater.
- Adjust dose based on the investigator's assessment.

Eltrombopag:

- Recommended Initial Dose: 50 mg once daily, taken orally 1 hour before or 2 hours after meals.
- Maximum Daily Dose: Not recommended to exceed 150 mg.

6.9.3.6. Endocrine Toxicities

During treatment, endocrine toxicities will be managed through interruption, discontinuation, or dose modification in accordance with Section 6.6, Table 8 and Table 9.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw from the study or discontinue study treatment at any time and for any reason without prejudice to their future medical care by the physician or at the institution. The investigator and/or sponsor can decide to withdraw a participant from the IP and/or other protocol-related procedures at any time for the reasons listed in this section. If study treatment is discontinued, the participant may remain in the study follow-up phase.

Discontinuation of the study at specific sites or of the entire study is detailed in Appendix 1.

7.1. Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety. See Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. If a participant discontinues treatment only, further evaluations and survival follow-up will be conducted.

Participants MUST discontinue the IP (and non-IP/non-IMP/AxMP) at the discretion of the investigator for any of the following reasons:

- Participants who are withdrawing consent from study intervention and/or study procedures/follow-up will be asked if they can continue to provide vital (survival) status remotely (eg, phone, email)
- Investigators may consider discontinuation of study intervention due to clinical deterioration while receiving active study intervention that indicates that continued participation in the study is not in the best interest of the participant.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE or SAE that requires more than 2 dose reductions, from the same drug-related AE or SAE, requires discontinuation.
- Participants who experience an AE requiring interruption of SI-B037 treatment may resume study treatment when the toxicity has resolved to Grade 1 or baseline within one treatment cycle (21 days) from the date of treatment interruption. Treatment may be resumed at the same dose level or at a reduced dose level in accordance with the protocol-defined dose modification guidelines.

  Note: participants who require interruption of SI-B037 dosing for more than 21 days due to treatment-related toxicity will permanently discontinue study treatment
- Any event that meets criteria for permanent discontinuation as described in Section 7.2.
- Documented unequivocal disease progression as defined by RECIST v1.1.

Note: Treatment beyond radiographic progression may be allowed if there is evidence of clinical benefit with continued therapy based on the investigator's judgment after discussing with the sponsor. Consent must be obtained.

- Start of anticancer therapy other than as outlined in this protocol.
- Termination of the study by the sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue the study. Strict conditions apply, and sponsor approval is required).
- Pregnancy (Section 8.5.5)
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc.). The investigator should discuss such issues with the medical monitor.
- Participant is lost to follow-up.
- Death.

All participants who discontinue study intervention should comply with protocol-specified procedures as outlined in the SOA (Section 1.3). The only exception is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate eCRF page.

7.1.1. Liver Toxicity Stopping Criteria

Whenever possible, timely confirmation of initial liver-related laboratory test result abnormalities should occur prior to reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria below must be reported as SAEs (Section 8.5). Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the following conditions:

- ALT or AST elevation >3 × ULN

AND

- Total bilirubin >2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

- No initial evidence of cholestasis, defined as ALP <2 x ULN

AND

- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease or the administration of other drug(s) know to be hepatotoxic

Discontinuation of intervention in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules may occur if the investigator believes that it is in best interest of the participant.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Dose Interruption

Refer to Section 6.6 for dose interruption.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

The reason (if available) for participant discontinuation or withdrawal from the study and the date of this decision must be recorded on the eCRF.

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The participant will be permanently discontinued from the study intervention and the study at that time. The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up and entered on the appropriate eCRF page.

At the time of discontinuing from the study, an EOT visit, as shown in the SOA (Table 1) should be completed. See the SOA (Table 1) for data to be collected at EOT visit and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected with the exception of OS data collected from public sources, as allowed by local regulations, the sponsor may retain and continue to use any data collected before the withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the study site records.

If vital status (whether the participant is alive or dead) is being measured, publicly available information (such as government vital statistics or obituaries) should be used to determine vital status only as appropriately directed in accordance with local law. The vital status data collected in this manner may be entered into the eCRF.

Participants who continue in a long-term follow-up may have already completed an EOT or early termination visit.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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, 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 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, the participant will be considered to have withdrawn from the study.
- Site personnel or an independent third party will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (Section 1.3). Adherence to the study design requirements, including those specified in the SOA, are essential and required for study conduct.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

Participants will be closely monitored for safety throughout the study. Urgent safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

8.1. Biomarker Assessments

Tumor tissue for all participants will be collected for tissue-based retrospective evaluation of PD-L1 expression per site local assessment with Roche Ventana PD-L1 IHC SP263 assay used per manufacturer's instructions and following agreement with the sponsor's medical monitor. All participants are required to provide tumor tissue blocks with FFPE or unstained FFPE tissue sections (10-12 slides of 4-5 µm thickness) to the central laboratory. If fewer slides are available, discussion with the medical monitor is required. FFPE tumor samples must be from primary or metastatic sites. A fresh biopsy is required if no archival/FFPE block or slides are available. VEGFR-2 (55B11, Cell Signaling Technology) and CD8 expression can be evaluated by IHC. Alternatively, multiplex IF panels incorporating PD-L1, CD8, VEGFR-2, CD31, FOXP3, CD68, and Ki67 may be used to characterize the tumor immune microenvironment and angiogenic profile.

Plasma will be collected to test for soluble VEGF-A and soluble PD-1 systemic levels. During the dose escalation phase (Part A) and dose finding phase (Part B), VEGF-A and PD-1 will be tested at C1D1 (predose and 2 hours post infusion), C1D2, C1D8, C1D15, C2D1, C3D1 (predose and 2 hours post infusion), C4D1 (predose and 2hrs post infusion), C4D15 and every D1 (predose) of subsequent odd cycles; additional blood collection time points may be prospectively adjusted based on preliminary biomarker data. These collection time points may be further refined based on the biomarker analysis results obtained during the dose escalation phase.

Additional exploratory blood-based translational biomarker assessments may be performed to further characterize the biological activity of SI-B037. Cytokine profiling may be performed to evaluate systemic immune activation and inflammatory responses associated with SI-B037 treatment.

NOTE: If no archival tissue is available and a fresh tissue biopsy is clinically contraindicated, please consult the sponsor.

8.2. Administrative and Screening Procedures

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reason(s) for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, complete blood count) and obtained before signing of the informed consent form (ICF) may be used for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SOA (Section 1.3).

8.3. Efficacy Assessments

Planned timepoints for all efficacy and immunogenicity assessments are provided as detailed in the SOA (Table 1) Table 2 and Table 3, as applicable.

8.3.1. Efficacy Assessments

Tumor response or efficacy assessments are summarized in Appendix 6. Tumor response will be evaluated using RECIST v1.1 criteria. For participants with melanoma, clinically visible cutaneous lesions should be assessed and documented throughout the study, as applicable.

A retrospective independent review of all submitted scans may be conducted at the discretion of the sponsor if needed. However, the results of this review will not be shared with investigators, and participant management will continue to be based solely on the investigator's assessment according to RECIST v1.1.

Enhanced CT (CT layer thickness less than 5 mm) or enhanced MRI is the preferred choice for tumor assessment. For participants allergic to CT contrast, a plain CT scan or enhanced MRI can be performed. For special lesions (such as skin lesions), only clinical examination is acceptable (relevant color photos shall be archived). The same imaging technique shall be applied throughout the study. If disease progression is suspected during the study, additional imaging examination can be performed at any time.

Baseline Imaging: Imaging examination at baseline shall inspect the neck (if clinically indicated), chest, abdomen, and pelvis and enhanced MRI of the brain. If the participant has received an imaging examination within 28 days prior to the first dose with satisfactory results, repeated examination may not be required. All participants shall undergo brain imaging examinations at baseline, preferably enhanced brain MRI. Thereafter, the brain MRI does not need to be repeated if no brain metastases were detected at baseline.

Efficacy analyses will include:

- ORR
- DCR
- DOR
- TTR
- PFS
- OS

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SOA (Table 1). Review of AEs and SAEs are described in Section 8.4.

- Physical examinations, including vital signs and weight
- AE, SAEs
- DLTs
- Deaths
- Study discontinuations
- Cardiac safety parameters
- Clinical laboratory abnormalities (Appendix 2)

8.4.1. Physical Examinations

A complete physical examination is performed at baseline and at EOT. A complete physical examination will include, at a minimum, assessments of the participant's general condition, head and face, cutaneous system, lymph nodes, eyes, ear nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal, nervous system, and mental state.

Targeted physical examinations are performed at Screening, Day 1 of every cycle, and safety visit. Targeted physical examination will include assessments of systems as judged by the investigator. If clinically indicated during other visits, a targeted physical examination (as judged by the investigator) will be performed.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.1.1. Weight and Height

Weight and height are measured during baseline. Only weight is measured on Day 1 of subsequent cycles. The initial drug dose is calculated using the weight measurement on Cycle 1 Day 1 (within a 1-day window). The window period for subsequent cycles is ±7 days. If during treatment, the participant's weight changes by ±10% of the baseline weight, the participant's dose will be recalculated based on the updated weight. For participants with a body weight ≥100 kg, the maximum administered dose will be capped at the dose calculated for a body weight of 100 kg to limit excessive exposure in participants with very high body weight.

8.4.1.2. Vital Signs

Vital signs including heart rate, blood pressure, oxygen saturation, respiration rate, and body temperature will be assessed according to the schedule in the SOA (Section 1.3).

On study treatment infusion days, vital signs should be assessed within 60 minutes prior to initiation of the infusion. If clinically indicated, the investigator may increase vital signs surveillance.

8.4.2. Cardiac Safety Parameters

All participants should undergo routine ECG monitoring using a 12-lead ECG.

Triplicate ECGs are to be performed as outlined in the SOA (Section 1.3). Triplicate readings should be completed within 5 minutes (1 to 3 minutes between readings). Routine ECG parameters include heart rate, pulse rate, QTcF, and QRS intervals (ΔHR, ΔPR, ΔQTcF, and ΔQRS). Preference should be to use an ECG machine that calculates the standard intervals automatically. In addition, QTc will be manually calculated using the Fridericia formula. Automated analyses reporting a prolongation of QTc should be read by a cardiologist to ensure accuracy of interpretation.

Record all ECG conditions and corresponding values of the ECG, including but not limited to heart rate, P-R interval, QRS interval, QT interval, QTc interval, etc.

- Cycle 1 Day 1: All participants should undergo routine ECG monitoring (triplicate reading, 1 to 3 minutes between readings, all 3 completed within 5 minutes) starting within 30 minutes before the first dose, within 15 minutes after the end of the infusion, then 2 hours ±30 minutes and 4 hours ±30 minutes after the end of the infusion via 12-lead ECG.
- For Cycle 1 Day 2, Day 3, Day 8, Day 15 and any subsequent Cycles: ECG monitoring should follow the PK blood collection schedule provided in Table 2 and Table 3.
- If clinically indicated, the investigator may add a 12-lead ECG reading. Repeat ECG as necessary if QTc >500 ms or 60 ms over baseline. ECG monitoring should follow the PK blood collection schedule provided in Table 2 and Table 3.
- For timepoints where both ECGs and PK/biomarker samples are collected, ECGs should be done within 30 minutes prior to the blood draw. On days other than Day 1 of any cycle, the ECGs should occur within 30 minutes prior to the PK blood draw (Table 2 and Table 3) if applicable.

8.4.3. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and the SOA (Table 1) for the timing and frequency of tests.

Screening: Laboratory assessments must be collected and reviewed within 28 days prior to randomization.

Treatment: For the first treatment visit, screening laboratory assessments need not be repeated if they were performed within 72 hours prior to dosing, the results are available and have been reviewed for eligibility. Onsite laboratory assessments/local laboratory testing should be performed within 48 hours prior to each dose or at a frequency consistent with the local SoC.

Follow-up: Laboratory assessments are to be performed at the Safety Follow-up Visit and may be repeated as clinically indicated.

Additional clinical laboratory tests may be performed at any time during the trial at the discretion of the investigator, if clinically indicated.

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be followed until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SOA (Table 1).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.4.4. Pregnancy Testing

Individuals of child bearing potential must have a negative pregnancy test prior to enrollment and within 24 hours (or up to 72 hours in situations where results cannot be obtained within the standard 24-hour window) prior to administration of study intervention on Day 1 of each cycle.

Highly effective contraception measures must be taken by participants in this trial from the first dose of SI-B037 through 7 months after the last dose of treatment to protect the health and safety of the mother and/or child. Despite the warnings provided and precautions taken, pregnancy may occur during research participation. Investigators must be aware of the requirements related to reporting and follow-up if a research participant's partner becomes pregnant.

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including at least 7 months after study intervention administration, the investigator must report the pregnancy of a participant or partner to the sponsor or its designee (within 24 hours of learning of the pregnancy), and the IRB (as required per institutional policy and protocol-specified reporting requirements), and include the following information: expected date of delivery, last menstruation, estimated conception date and pregnancy result (if known).

If a participant becomes pregnant while receiving SI-B037, the IP will be discontinued permanently.

When reporting pregnancy please note the following:

- Pregnancy should be reported as “Information” (not as an “AE” or “Other Problem or Event”).
- Pregnancy does NOT have to be reported to the IRB if the participant is receiving follow-up only, and conception occurred outside of the time-period that the study protocol requires for contraception (ie, 3 months after the last dose of the study drug and the pregnancy occurred after that time).
- Subsequent reports containing follow-up information regarding a pregnancy are not required unless the pregnancy results in a congenital anomaly. The congenital anomaly should be promptly reported.
- If you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child, it must be reported to the sponsor.

Although pregnancy itself is not considered an AE or an SAE, the participant or partner of a male participant should be followed until termination or to term to ensure absence of congenital anomaly or birth defect that may have resulted from maternal exposure or transmission of the study drug via semen following paternal exposure.

8.5. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Disease-related events/Outcomes and Other Events/Procedures do not qualify as AE or SAE. The terms disease progression, progression of disease or malignant disease progression and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only. Clinical symptoms of progression that cannot be determined as reasonably due to progression of the underlying malignancy or do not fit expected pattern of progression for the disease under study should be reported as an AE or SAE.

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

TEAEs will be followed until 30 days after discontinuation; AESI or TRSAE will be followed until 60 days after discontinuation. TEAEs that are ongoing at the safety follow-up, will be followed until resolve or study discontinuation, or patient withdraw, or loss of follow-up, whichever is later as specified in the SOA (Table 1).

AEs that occur after the ICF is signed but before the first dose of IP should be recorded as medical history unless the AE is related to a study procedure.

At each study visit, the investigator or qualified designee will inquire about the occurrence of AEs since the last visit. The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 4.

The investigator must report any SAE that is believed to be related to the IP or protocol-specified procedure (eg, a follow-up biopsy).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Any fatal AE (Grade 5) must be recorded as an SAE (with the exception of death directly caused by disease progression), regardless of its relationship to the study intervention or the timing of its occurrence, until the end of the study. Such events must be reported to the sponsor by SAE reporting instructions described in Appendix 4.

Disease progression (of the underlying disease being studied), which is a study endpoint, should not be reported as an AE or SAE. However, diagnosis of AE/SAE due to complications resulting from disease progression may be reported as an individual term if it fulfills the AE/SAE definition.

All second and primary malignancies/new malignancies of any Grade, regardless of relationship to study treatment, must be reported as SAEs, from the time of signing the ICF until the end of the study.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the sponsor.

8.5.2. Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Inquiries about specific AEs will be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

Participants will be instructed regarding direct reporting of AEs at each visit, and participants will be queried if evidence of an AE is recorded. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. Baseline conditions that worsen after the first dose of IP/IMP/Non-IP/Non-IMP during the study will be recorded as AEs. 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 to be performed.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All AEs will be followed to adequate resolution or clinical stability, as follows:

- AEs ongoing at the EOT visit will be followed up as long as necessary to adequately evaluate the participant's safety or until the event stabilizes, at least 30 (±7) days after the last administration of SI-B037 or start of new non-protocol anticancer therapy (NPACT), whichever comes first.
- Treatment-related AEs presenting during the EOT visit will be followed for at least 60 days.
- SAEs will be followed until the condition resolves or there is a return to baseline, or until start of new NPACT as noted in Appendix 4.

Nonserious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study intervention (Section 7.1). AEs ongoing at the final visit will be followed up for as long as necessary to adequately evaluate the participant's safety or until the event stabilizes, and SAEs will be followed until resolution.

After the Safety Follow-up Visit, only SAEs that are related to the study drug will be followed and reported to sponsor.

Further information on follow-up procedures is provided in Appendix 4.

8.5.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A suspected unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements. Upon receipt of an SAE report, the sponsor will evaluate for qualifying SUSARs and report them to the applicable health authorities within the time frame required by local applicable laws and regulations. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators within 15 days.

8.5.5. Pregnancy

Individuals of child bearing potential must have a negative pregnancy test prior to randomization and within 24 hours (or up to 72 hours in situations where results cannot be obtained within the standard 24-hour window) prior to administration of study intervention on Day 1 of each cycle. Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [hCG] to be performed every 12 weeks (±1 week) for 3 months after the last dose of study intervention is required. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

Highly effective contraception measures must be taken by participants in this trial from the first dose of SI-B037 through 7 months after the last dose of treatment to protect the health and safety of the mother and/or child. Despite the warnings provided and precautions taken, pregnancy may occur during research participation. Investigators must be aware of the requirements related to reporting and follow-up if a research participant's partner becomes pregnant.

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including at least 7 months after study intervention administration, the investigator must report the pregnancy of a participant or partner to the sponsor or its designee (within 24 hours of learning of the pregnancy), and the IRB (as required per institutional policy and protocol-specified reporting requirements), and include the following information: expected date of delivery, last menstruation, estimated conception date and pregnancy result (if known).

If a participant becomes pregnant, SI-B037 will be discontinued permanently.

When reporting pregnancy please note the following:

- Pregnancy should be reported as "Information" (not as an "AE" or "Other Problem or Event").
- Pregnancy does NOT have to be reported to the IRB if the participant is receiving follow-up only, and conception occurred outside of the time-period that the study protocol requires for contraception (ie, 3 months after the last dose of the study drug and the pregnancy occurred after that time).
- Subsequent reports containing follow-up information regarding a pregnancy are not required unless the pregnancy results in a congenital anomaly. The congenital anomaly should be promptly reported.
- If you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child, it must be reported to the sponsor.

Although pregnancy itself is not considered an AE or an SAE, the participant or partner of a male participant should be followed until termination or to term to ensure absence of congenital anomaly or birth defect that may have resulted from maternal exposure or transmission of the study drug via semen following paternal exposure.

8.5.6. Cardiovascular and Death Events

Information on cardiovascular events and reporting deaths is provided in Section 8.4.2, Section 8.5.1, and Appendix 4.

8.5.7. Adverse Events of Special Interest

The study drug has the potential risk of causing AESIs based on preclinical findings and information associated with other drugs in the same category. Information on AESIs is provided in Appendix 8.

8.5.8. Infusion-Related Reactions (IRR)

IRRs are defined as symptoms that occur during and within the first 6 hours after the infusion of study treatments. Symptoms can include fever, chills, rigors, arthralgias, myalgias, urticaria, pruritus, rash, diaphoresis, hypotension, dizziness, syncope, hypertension, dyspnea, cough, and wheezing, as well as severe hypersensitivity reactions including anaphylactic reactions. Grade 3 and Grade 4 IRRs can include severe or clinically significant cardiopulmonary events and severe allergic reactions such as symptomatic bronchospasm and anaphylactic reactions. Additional information is provided in Section 6.9.3.1.

8.6. Pharmacokinetics

PK assessments are detailed in the SOA Table 1, Table 2 and Table 3, as applicable and include the following:

Parameters

- Serum concentration of SI-B037
- Serum PK parameters will include maximum (peak) observed concentration in serum (C_{max}), T_{max}, area under the serum concentration-time curve from time 0 to 8 hours ($AUC_{0–8}$), area under the serum concentration-time curve up to the last quantifiable time (AUC_{last} or AUC_{tau}) and, if possible, terminal elimination rate constant (K_{el}), elimination half-life ($t_{1/2}$), clearance (CL), volume of distribution after a single dose (V_z), apparent volume of distribution at steady-state after multiple doses (V_{ss}) of total SI-B037 antibody.

These PK parameters will be assessed as data permits. Drug-drug interactions will be assessed. Any remaining blood samples from PK testing can be used for relevant ligand detection for retrospective exploratory studies. Further, PK data from this study may be combined with data from other studies for population PK analysis, with results reported separately

These PK parameters will be calculated after the first dose and after multiple doses if applicable.

8.7. Pharmacodynamics

Exploratory pharmacodynamic assessments may be performed to characterize the biological activity of SI-B037 and evaluate evidence of target engagement, immune modulation, and modulation of angiogenic pathways. As described in Section 8.1, these assessments may include

analyses of circulating angiogenic biomarkers (e.g., VEGF-A and other soluble proteins), cytokine profiling, and tissue-based biomarker analyses, where available. Biomarker data may be summarized descriptively and explored in relation to pharmacokinetic exposure, safety, immunogenicity, and preliminary antitumor activity to support characterization of the pharmacologic effects of SI-B037.

8.8. Genetics

Genetics will not be a part of the study.

8.9. Immunogenicity Assessments

Immunogenicity assessments will be performed to evaluate the incidence and characteristics of ADA against SI-B037 as specified in the SOA, (Section 1.3) and PK/Immunogenicity sampling schedules (Table 2 and Table 3).

Serum samples will be collected at the protocol-defined timepoints to evaluate baseline and treatment-emergent ADA responses. Samples may be analyzed using validated or qualified multi-tier immunogenicity assays, including Screening, confirmatory, titer, and, where appropriate, neutralizing antibody (NAb) assays.

Immunogenicity results will be summarized descriptively, including the incidence of baseline-positive and treatment-emergent ADA responses, ADA titers, persistence, and the occurrence of neutralizing antibodies, when evaluated. The potential relationship between ADA status and pharmacokinetics, pharmacodynamic biomarkers, safety, IRRs, hypersensitivity reactions, and preliminary antitumor activity may be explored.

Detailed assay methodologies, sample handling procedures, assay cut points, confirmatory criteria, neutralizing antibody testing strategies, and data analysis methods will be described in the applicable Bioanalytical Analysis Plan, Immunogenicity Analysis Plan, and statistical analysis plan (SAP).

Samples may be stored for up to 10 years after the end of the study or the maximum period allowed by applicable law to enable further analysis of immune responses to SI-B037. Samples may be used or archived for other bioanalytical assessments and/or for additional method purposes, if the need arises and to the extent possible.

9. STATISTICAL CONSIDERATIONS

The final analysis will occur after all participants have either discontinued the study or completed their last study visit or contact.

9.1. Statistical Hypothesis

No hypotheses will be formally evaluated in this study.

9.1.1. Multiplicity Adjustment

No multiplicity adjustment is needed for this study.

9.2. Analysis Sets

For the purposes of analysis, the following populations are defined in Table 12.

Table 12 Study Analysis Sets

Analysis Set	Description
Safety analysis set (SAS)	All enrolled participants that receive at least 1 dose of study drug.
DLT-evaluable set	Participants enrolled in dose escalation phase who experienced DLTs and those who did not experience DLTs but completed the first cycle of study.
Pharmacokinetics	All enrolled participants at least 1 dose of study drug and with any available concentration-time data.
Immunogenicity	All enrolled participants at least 1 dose of study drug and with baseline assessment and at least 1 follow-up assessment.

Abbreviations: DLT=dose-limiting toxicity; EOT=end of treatment; SAS=safety analysis set

9.3. Statistical Analyses

9.3.1. General Considerations

The SAP will provide a comprehensive, technical, and detailed description of all planned statistical analyses. The SAP will be finalized prior to the database lock or interim analysis if applicable.

Descriptive statistics will be provided for selected demographic data, safety, efficacy, and PK data by dose cohort and time as appropriate.

Unless stated otherwise, descriptive statistics on continuous data will include means, medians, standard deviations, and ranges (as well as geometric means and geometric coefficient of variation for some PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

9.3.2. Safety Analyses

The primary objective is to determine the safety and tolerability of SI-B037, and the primary endpoints include DLTs, SAEs, AESI, TEAEs, death, TEAE leading to discontinuation, ECOG PS, and other safety findings.

Based on the DLT-evaluable set, DLTs, as defined in the protocol, will be summarized by category and dose level.

Unless otherwise specified, the safety analyses will be based on the SAS. The raw data will be listed. The treatment period for the safety analysis is defined as the time from the first dosing of the study drug to within 30 days after the last administration.

AEs will be coded using the MedDRA v29.0 or higher. The severity of AEs will be graded according to CTCAE v6.0.

The incidence of AEs will be summarized based on treatment groups by SOC and PT term. When calculating the incidence of AEs, it will be counted once if the same subject experienced the same AE multiple times and the most severity of AE Grade will be used.

If the AE Grade is missing, or relationship is missing, please refer to the study SAP for details.

9.3.3. Efficacy Analyses

Efficacy analyses will be performed using the SAS set. Descriptive statistics will be provided for ORR, DCR, duration of response (DOR), PFS, and OS. The ORR and its 95% confidence interval for each dose group will be calculated using the exact Clopper-Pearson method. Best overall response will be summarized. Median DOR, PFS, and OS, along with their corresponding 95% CIs, will be estimated using the Kaplan-Meier method for each dose group. Detailed methodology and analysis will be provided in SAP.

9.3.4. Other Analyses

Any other analysis will be provided in detail in SAP.

9.4. Interim Analyses

Interim analysis for futility will be performed to Part C. The Simon two-stage design (Simon 1989) will be applied for futility analysis. For each cohort in Part C, the null hypothesis is that the true overall response rate is 5%, and the alternative hypothesis is that the true overall response rate rate is 15%. In Stage 1, a total of 20 participants will be enrolled at each RDE. If there are no responders (CR/PR) in these 20 participants, the sponsor will consider stopping the study for futility. Otherwise, the additional 20 participants will be enrolled in Stage 2, resulting in a total sample size of 40 at each RDE. The null hypothesis will be rejected if there are 4 or more responders (CR/PR) observed at the end of Stage 2 among these 40 participants.

This design yields a 1-sided type I error rate of 13.24% and a power of 85.62%.

The decision to terminate enrollment, continue the study as planned, or otherwise modify study conduct will be based on a review of the totality of available data. This review may include the observed response rate and its uncertainty, the magnitude and durability of observed responses,

timing and maturity of response assessments, safety, and other available measures of clinical activity, relevant disease and indication characteristics, and the overall benefit-risk profile.

Thus, the Simon two-stage futility boundary will serve as an important prespecified statistical criterion to inform decision-making; however, the final decision regarding study termination will be based on the totality of the available evidence and clinical judgment

9.5. Sample Size Determination

Approximately 18 DLT-evaluable participants are enrolled in the dose escalation phase to estimate one or more RDEs.

Approximately up to 20 participants will be enrolled for each selected dose in the dose finding phase.

Approximately up to 40 participants will be randomized by RDE 1 or RDE2 for each tumor type. Approximately up to 320 participants will be enrolled in dose expansion phase.

10. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative (LAR) and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection 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 participant 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.
- Participants must be reconsented 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 participant or their LAR
- Participants who are rescreened are required to sign a new ICF.
- The ICF contains details that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Recruitment Strategy

A participant recruitment program will be developed and implemented in line with country requirements to assist sites with recruitment efforts. Tactics will support participant education and awareness and health care provider outreach. This program will also include solutions to address anticipated recruitment challenges. The recruitment strategy and tools to be used are included in the country application dossier or subsequently, as a non-substantial amendment, if they are added after the initial application is submitted or approved.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure

must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

Committees Structure

An SMC will be assembled for this global study and will follow the SMC charter. The committee will consist of experts including clinicians, statisticians, ethicists, and patient advocates. The SMC will regularly review unblinded data during the trial and monitor safety and efficacy. The committee will make recommendations based upon their review of the data.

Participant safety will be continuously monitored by the sponsor and the SMC, which includes safety signal detection at any time during the study.

Before initiation of the study at any site, the local lead investigator must have written and dates approval from the appropriate IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials, and all other written information provided to participants. The investigator, sponsor, or designee should provide the IRB/IEC with reports, updates, and other appropriate or requested information annually, or more frequently in accordance with regulatory or institutional requirements.

Dissemination of Clinical Study Data

To benefit potential study participants, patients, health care providers, and researchers and to help the sponsor honor its commitments to study participants, the sponsor will make information about clinical research studies and a summary of their results available to the public per regulatory and the sponsor's requirements. The sponsor will post-study information on local, national, or regional databases in compliance with national and international standards for disclosure. The sponsor may voluntarily disclose information to applicable databases. In the EU, the summary of results and summary for laypersons will be submitted within 1 year of the end of the trial in the EU/European Economic Area and third-world countries.

Data Quality Assurance

Data collection is the responsibility of the clinical study 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.

Data for this study will be recorded via an EDC system using web-based eCRFs. Data will be transcribed by the site from source documentation into the eCRF. Accurate and reliable data collection will be assured by verification and crosscheck of the eCRFs against the investigator's records by the site monitor (source document verification following in accordance with GCP and the ICH E6 GCP Guideline).

A comprehensive validation check program utilizing front-end checks in the eCRF will verify the data and discrepancies will be generated accordingly in the eCRF for online resolution by the investigator at the site.

In addition, the eCRF data will be reviewed on an ongoing basis for medical and scientific plausibility.

Guidance on completion of eCRFs will be provided in the eCRF completion guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the CRF completion guidelines.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in the clinical monitoring plan
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected 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:

For Study Termination:

- Discontinuation of further study intervention development

For Site Termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- 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 International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. CLINICAL LABORATORY TESTS

Conduct the clinical laboratory tests as indicated in the schedule of assessments (Section 1.3). Protocol-required lab tests are listed in Table 13.

Table 13 Protocol-Required Laboratory Tests

Laboratory Tests	Parameters
Hematology	• CBC with differentials – WBC count with differential ▪ WBCs ▪ Neutrophils ▪ Lymphocytes ▪ Monocytes ▪ Eosinophils ▪ Basophils – RBC count – MCV – Hemoglobin – Hematocrit – Platelet count • Reticulocytes
Clinical chemistry	• Sodium • Potassium • Chloride • Bicarbonate • Blood urea nitrogen or serum urea • Creatinine • Creatinine clearance (Cockcroft-Gault equation) • Calcium • Magnesium • Phosphorus • Glucose (fasting ≥6 hours at Screening only, all other glucose labs do not require fasting) • Total cholesterol • Triglycerides • AST/SGOT • ALT/SGPT • GGT • ALP [a] • Total bilirubin • Direct bilirubin • Total protein • Albumin • Lactate dehydrogenase
Coagulation function	• PT • INR • aPTT • Fibrinogen
Cardiac markers	• B-type natriuretic peptide (BNP) or pro-BNP • Troponin I (preferred) or troponin T, as available at the institution [b]
Thyroid function	• TSH • Free T3 • Free thyroxine (T4)
Routine urinalysis	• pH • Glucose • Protein • Blood

Laboratory Tests	Parameters
	• Ketones • Leukocyte esterase • Nitrates • RBC • WBC • Bacteria
Pregnancy testing	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for IOCBP) [c] • FSH [d]
PK testing [e,f,g]	• SI-B037 (serum concentration) • Total SI-B037 antibody (serum concentration)
Immunogenicity	• ADA [f]
Virology	• Hepatitis B core antibody (HBcAb) • Hepatitis B surface antibody (HBsAb) • Hepatitis B surface antigen (HBsAg) • Patients with evidence of HBV infection will need HBV DNA viral load testing (at Screening and repeated as clinically indicated) • Hepatitis C antibody and HCV-RNA (at Screening and repeated as clinically indicated) • HIV testing and CD4 count unless contraindicated per local laws/ regulations (at Screening only and repeated as clinically indicated). For patients with known HIV, HIV viral load, and CD4 count should be evaluated for eligibility

Abbreviations: ADA=anti-drug antibody; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; GOT=glutamic oxaloacetic transaminase; GGT=gamma-glutamyl transferase; GPT=glutamic pyruvic transaminase; INR=International Normalized Ratio; IOCBP=individuals of childbearing potential IRB/IEC=Institutional Review Board/Institutional Ethics Committee; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PK=pharmacokinetic; RBC=red blood cell; TSH=thyroid stimulating hormone; WBC=white blood cell.

a. If alkaline phosphatase is elevated, consider fractionating.
b. Troponin I or troponin T is the only cardiac laboratory test that sites should have results for before treating participants on Day 1.
c. Serum testing will be used at Screening. A serum or urine pregnancy test is performed every even-numbered cycle starting with Cycle 2. If pregnancy is suspected during the study, an additional serum/urine pregnancy test should be performed and the sponsor notified.
d. Postmenopausal status in female participants <55 years old must be confirmed by serum follicle stimulating hormone (FSH) test at Screening, unless they have undergone hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
e. PK samples: Collect pre- and post infusion samples on Day 1.
f. Collect pre-infusion PK samples simultaneously with all immunogenicity (ADA) samples in Cycles 1, 2, 3, 4, 5, 7, 9, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and EOT.
g. For unscheduled visit, a PK blood sample will be collected with a routine ECG.

APPENDIX 3. NCI-CTCAE VERSION 6.0

This file can be downloaded at the following website:

http://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v6.pdf

(Accessed August 3, 2026.)

APPENDIX 4. AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's LAR who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring hospitalization, emergency room visit or visit to/by a healthcare provider). The participants/participant's LAR will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participants/participant's LAR concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participants/participant's LAR will be collected during an interview with the participants/participant's LAR and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the Adverse Event Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant 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.

- Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Other situations:

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

Recording and Follow-Up of AE and/or SAE

Recording Adverse Events and Serious Adverse Events:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will use CTCAE v6.0 to make an assessment of intensity for each AE and SAE reported during the study. CTCAE uses Grades to refer to the severity of the AE. The CTCAE displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guideline.

- **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 instrumental activities of daily living (ADL) or mild/moderate impact on age-appropriate normal daily activity
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL or severe impact on age-appropriate normal daily activity
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- Suggested bullet in variable blue text may not be required for studies where death is an endpoint.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reporting of SAEs

All SAEs must be reported within 24 hours of the investigator becoming aware of the event, using the electronic case report form system that will automatically inform the SystImmune designee. If the electronic reporting system is not accessible within those 24 hours, paper SAE report forms can be used and sent to:

Pharmacovigilance Contact	Medical Monitor
drugsafety@systimmune.com	Medical monitor designee

IF THE SERIOUS ADVERSE EVENT IS FATAL OR LIFE-THREATENING, THE SPONSOR MUST BE INFORMED IMMEDIATELY.

Instructions for Reporting SAEs and Completion of the SAE eCRF:

- Complete all sections. Provide as much information as possible.
- Where there is a choice of response, please complete the appropriate box with an "X."
- Enter all dates in the format DD/MMM/YYYY (eg, 01/MAY/2021).

APPENDIX 5. CONTRACEPTIVE AND BARRIER GUIDANCE

In inclusion criteria (Section 5.1), sexually active fertile participants and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and until the end of relevant systemic exposure, defined as 7 months for IOCBP and 4 months for men, after the last dose of study treatment.

The effect of SI-B037 on the PK of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as "effective methods of contraception," they should be used together with another method.

Contraception Guidance for Female Participants of Childbearing Potential

One of the highly effective methods of contraception listed below, in combination with 1 acceptable barrier method below, is required during study duration and until the end of relevant systemic exposure, defined as 7 months after the last dose of study treatment. Local laws and regulations may require the use of alternative and/or additional contraception methods.

Female participants of childbearing potential should refrain from egg retrieval procedures for the duration of the study treatment and until 7 months after the last dose of study treatment.

Highly Effective Contraceptive Methods That Are User Dependent:

These methods have a failure rate of <1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
  - Oral, intravaginal, or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation.
  - Oral or injectable.

Highly Effective Contraceptive Methods That Are User Independent:

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system.
- Intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner

  - A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female participant of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence
  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - Female participants of childbearing potential who choose complete abstinence must continue to have pregnancy tests per the protocol. Acceptable alternate methods of highly effective contraception must be discussed in the event that any of these participants choose to forego complete abstinence.

Acceptable Barrier Methods for Use in Combination with a Highly Effective Method:

- Male or female condom with or without spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide

Unacceptable as a Sole Method of Contraception:

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Progestogen-only oral hormonal contraception of which inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (eg, calendar, symptothermal, postovulation methods)
- Withdrawal (eg, coitus interruptus)
- Spermicide only
- Lactation amenorrhea method

Contraception Guidance for Male Participants with Partner(s) of Childbearing Potential

Male participants with female partners of childbearing potential are eligible if they agree to the following during the treatment and until the end of relevant systemic exposure, defined as 4 months after the last dose of study treatment.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom during study duration and until end of relevant systemic exposure, defined as 4 months after the last dose of study treatment.
- Female partners of male participants in the study should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 4 months after the last dose of treatment in the male participant.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 4 months after the last dose of study treatment.

Refrain from donating sperm for the duration of the study treatment and until 4 months after the last dose of study treatment.

APPENDIX 6. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST V1.1)

Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- CT is the best currently available and reproducible method to measure lesions selected for response assessment. PET/CT that has diagnostic CT is acceptable; however, a fluorodeoxyglucose-positron emission tomography (FDG-PET) is not acceptable. MRI is also acceptable in certain situations (eg, for body scans but not for lungs).
- Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Ultrasound should not be used to measure tumor lesions.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete response.
- Cytology and histology can be used in rare cases (eg, for evaluation of residual masses to differentiate between partial response [PR] and complete response [CR] or evaluation of new or enlarging effusions to differentiate between progressive disease [PD] and response/stable disease [SD]).
- Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

Baseline Disease Assessment

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness)

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non- measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.

"Cystic lesions" thought to represent cystic metastases can be considered measurable 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.

Non-Measurable Lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Blastic Bone Lesions

Blastic bone lesions are non-measurable.

Lesions With Prior Local Treatment

Lesions with prior local treatments such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed.

The 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, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-Target Lesions

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required, and they should be followed as "present," "absent," or in rare cases, "unequivocal progression."

Response Criteria

Evaluation of Target Lesions

Evaluation of target lesions is provided in Table 14.

Table 14 Evaluation of Target Lesions

Response	Description of Response
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive disease (PD)	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

Special Notes on the Assessment of Target Lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis of <10 mm.

Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure," in which case a default value of 5 mm should be assigned.

Lesions that split or coalesce on treatment. When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Table 15 Evaluation of Non-Target Lesions

Response	Description of Response
Complete response (CR)	Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive disease (PD)	Unequivocal progression of existing non-target lesions. When the participant has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. When the participant only has non-measurable disease. There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized too widespread.

Abbreviations: CR=complete response; PD=progressive disease; SD=stable disease

New Lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the participant's baseline lesions show PR or CR).
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is PD based on a new lesion.

No FDG-PET at Baseline and a Positive FDG-PET at Follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Time Point Response

A summary of the overall response status calculation at each time point for participants who have measurable disease at baseline is presented in Table 16.

Table 16 Time Point Response: Participants with Target (±Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/or not all evaluated	No	PR
SD	Non-PD/or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable

When participants have non-measurable (therefore non-target) disease only, Table 17 is to be used.

Table 17 Time Point Response: Patients with Non-target Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
PD	Yes or No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable.

a. Non-CR/ non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials. To assign this category when no lesions can be measured is not advised.

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, (ie, in randomized Phase 2 or 3 trials or studies where SD or progression are the primary endpoints), confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies, which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Missing Assessments and Unevaluable Designation

When no imaging/measurement is done at all at a particular time point, the participant is not evaluable at that time point.

If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

APPENDIX 7. ECOG PERFORMANCE STATUS SCALE

The ECOG Performance Status Scale is provided in Table 18.

Table 18 Eastern Cooperative Oncology Group Performance Status Measurement (ECOG) Scale

Grade	Measurement Criteria
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX 8. SI-B037 ADVERSE EVENTS OF SPECIAL INTEREST

Clinical Category	Adverse Event	Grade
Immune related toxicities	Immune related AEs (including but not limited to pneumonia, colitis, hepatitis, dermatitis/severe rash, nephritis, endocrinopathies, myocarditis, myositis, encephalitis, thyroiditis, uveitis, thrombocytopenia)	≥ Grade 2 (or symptomatic/treatment-requiring for endocrinopathies)
Hypersensitivity / infusion reactions	Infusion-related reaction or hypersensitivity reaction	≥ Grade 3
	Systemic allergy / severe type 1 hypersensitivity	Any severe event
Pulmonary toxicity	Interstitial lung disease (ILD) / pneumonitis	Any Grade
Cardiovascular toxicity	Hypertension	≥ Grade 3
	Left ventricular dysfunction / congestive cardiac failure	≥ Grade 3
Thromboembolic events	Venous thromboembolic events (VTE)	≥ Grade 3
	Arterial thromboembolic events (ATE)	≥ Grade 3
Neurologic vascular toxicity	Posterior reversible encephalopathy syndrome (PRES/RPLS)	≥ Grade 3
Renal toxicity	Proteinuria	≥2 g/24 h
	Nephrotic syndrome, renal insufficiency, or renal failure	≥ Grade 3
Bleeding / hemorrhagic events	Bleeding / hemorrhage	≥ Grade 3
Gastrointestinal toxicity including wound healing complications	GI perforation, fistula, or wound healing complication	≥ Grade 3
	Diarrhea	≥ Grade 3

Abbreviations: AE=adverse events; AESI=adverse events of special interest; GI=gastrointestinal

APPENDIX 9. BAYESIAN TOXICITY MONITORING FOR EXCESSIVE TOXICITY

The Bayesian Toxicity Monitoring (BTM) approach (Lee et al. 2025) will be applied in the dose expansion phase. Monitoring will begin once at least 10 participants within a cohort have received study treatment.

The Bayesian monitoring framework will evaluate:

- Grade ≥ 3 Treatment-related serious adverse events (TRSAEs).
- Grade ≥ 3 Treatment-related adverse events resulting in treatment discontinuation, treatment interruption, or other clinically significant treatment modification.

The monitoring will employ a Bayesian model using a non-informative prior distribution of Beta (0.5, 0.5).

A cohort may be considered to have an unacceptable toxicity profile if:

- the posterior probability that the true incidence of Grade ≥ 3 TRSAEs exceeds 35% is greater than 0.90; or
- the posterior probability that the true incidence of Grade ≥ 3 treatment-related adverse events resulting in treatment discontinuation or clinically significant treatment modification exceeds 40% is greater than 0.90.

Crossing a boundary will not automatically result in an enrollment pause. It will trigger a comprehensive review of available safety, efficacy, pharmacokinetic, pharmacodynamic, and participant-level data by the sponsor and the applicable Safety Review Committee. Decisions regarding ongoing enrollment will be based on the totality of available evidence and the overall benefit-risk profile.

The stopping boundaries for Grade ≥3 TRSAEs and Grade ≥3 TRAEs leading to treatment discontinuation or clinically significant treatment modification are presented in Table 19 and Table 20. Additional details of the Bayesian monitoring methodology will be provided in the SAP.

Table 19 Stopping Boundaries for G3+ TRSAEs

Participants Dosed	Participants with at Least 1 Excessive Toxicity Event
10	6+
15	8+
20	10+
25	12+
30	14+
35	16+
40	18+

Table 20 Stopping Boundaries for G3+ TRAEs leading to treatment discontinuation or clinically significant treatment modification

Participants Dosed	Participants with at Least 1 Excessive Toxicity Event
10	6+
15	9+
20	11+
25	14+
30	16+
35	18+
40	20+

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