Stemline Therapeutics, Inc.

A Phase 1, Open-label, Dose-escalation Study of the PI3K Inhibitor SL-901 in Patients with Advanced Solid Tumors

Protocol Number: STML-901-0119

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

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PROTOCOL SIGNATURE PAGE

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Investigator Statement

I understand that all documentation provided to me by the Sponsor or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Ethics Committee (EC)/Institutional Review Board (IRB) and national regulatory approval. No changes will be made to the study protocol without the prior written approval of the Sponsor and the EC/IRB, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood and agree to abide by all the conditions and instructions contained in this protocol.

Principal Investigator:

Print Name	
Signature & Date	
Institution	

Stemline Therapeutics, Inc:

Print Name	[redacted]
Signature & Date	[redacted]
Title	[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AKT (PKB)	RAC-alpha serine/threonine-protein kinase (protein kinase B)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BID	Twice daily
BP	Blood pressure
C	Cycle
CFR	Code of federal regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRA	Clinical Research Associate
eCRF	Electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA-PK	Deoxyribonucleic acid-dependent protein kinase
DOCR	Duration of complete response
DOR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOT	End-of-Treatment
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GPCR	G protein coupled receptors
GSK3	Glycogen synthase kinase 3
HDPE	High-density polyethylene
HED	Human equivalent dose
IC_{50}	50% inhibitory concentration

Abbreviation	Description
ICF	Informed consent form
ICH	International Council for Harmonisation
IME	Important medical event
IRB	Institutional review board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NFG	Non-fasting glucose
NOAEL	No observed adverse effect level
ORR	Objective response rate
OS	Overall survival
p-AKT	Phosphorylated-RAC-alpha serine/threonine-protein kinase (protein kinase B)
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PFS	Progression-free survival
p-GSK3	Phosphorylated glycogen synthase kinase 3
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol diphosphate
PIP3	Phosphatidylinositol triphosphate
PK	Pharmacokinetics
p-p70S6K	Phosphorylated p70S6 kinase
PR	Partial response
PT	Preferred term
PTEN	Phosphatase and tensin homolog
QC	Quality control
QD	Once daily
RBC	Red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RTK	Receptor tyrosine kinase
SAE	Serious adverse event

Abbreviation	Description
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:	A Phase 1, Open-label, Dose-escalation Study of the PI3K Inhibitor SL-901 in Patients with Advanced Solid Tumors
Protocol Number:	STML-901-0119
Study Phase:	Phase 1
Study Centers:	Approximately 25 centers in the United States, United Kingdom and Europe
Study Population	In Part 1a, patients with advanced solid tumors, to determine the regimen for Part 1b. In Part 1b, the clinical activity of SL-901 will be evaluated in patients with advanced solid tumors known to have specific genetic alterations, who may derive benefit from treatment with a phosphoinositide 3-kinase (PI3K) inhibitor.
Study Objectives:	This is a two-part study: In Part 1a, escalating doses and 2 schedules (once daily [QD] and twice daily [BID]) of SL-901 will be evaluated. In Part 1b, the clinical activity of SL-901 at the selected dose and schedule will be evaluated. **Primary Objective:** 1) To identify the maximum tolerated dose (MTD) of SL-901. 2) To identify an appropriate dosing regimen for further investigation of SL-901. 3) To characterize the pharmacokinetics (PK) profile of SL-901. 4) To generate clinical safety data and perform initial assessment of the safety profile of SL-901. **Secondary Objectives:** 1) To characterize the pharmacodynamics (PD) of SL-901 in blood and tissue. 2) To assess preliminary clinical activity of SL-901.
Study Design:	This clinical study includes 2 parts: 1) Part 1a: An open-label, dose-escalation and regimen-finding to investigate the safety, PK, and PD of SL-901 in patients with advanced solid tumors. In Part 1a, adverse events (AEs) occurring during the first cycle of treatment will be considered for the assessment of dose-limiting toxicities (DLTs), with continued evaluation of AEs in subsequent treatment cycles for further characterization of the safety of SL-901. This part will follow a 3+3 dose-escalation design to determine the MTD of SL-901 when administered on each a QD and BID schedule; single and multiple dose PK assessments will be performed to characterize the exposure of SL-901. 2) Part 1b: Up to 4 expansion cohorts of patients with specific genetic alterations that may derive benefit from treatment with a PI3K inhibitor will be treated SL-901 with the dose regimen selected in Part 1a. This study will explore different dose levels and schedules of SL-901 given as a single agent, therefore the term “regimen” is comprised of the

	unit dose administered and the specified schedule of dosing in a given cohort. A treatment cycle is 28 days, with daily dosing throughout the cycle. • In Part 1a, 3 to 6 patients may be enrolled in each regimen to be investigated. Schedules will include QD or BID administrations, as described in Table 5 for each specified dose level. • In Part 1b, 6 to 12 patients may be enrolled in each expansion cohort (up to 4 expansion cohorts may be opened for enrollment). Patients may continue to receive SL-901 until disease progression or unacceptable toxicity. **Dose-Escalation Rules:** In Part 1a of the study, AEs occurring during the first cycle of treatment will be considered for the assessment of DLTs, with continued evaluation of AEs in subsequent treatment cycles for further characterization of the safety of SL-901. Further assessment of the safety of SL-901 at the recommended regimen from Part 1a will be performed in Part 1b. Upon occurrence of a DLT in the first 3 patients of a given cohort dosing schedule, up to 3 additional patients will be added to that cohort dosing schedule. In the resulting 6-patient cohort dosing schedule, dose-escalation to a higher dose will occur when all 6 patients in that dosing schedule have completed the first cycle of SL-901, and no additional DLTs have occurred. If two or more DLTs occur in a given cohort dosing schedule, a DLT is established and the next lower dose level will be declared the MTD for that dosing schedule. See Section 6.4.2 for DLT definition. All dose-escalation steps and schedule recommendations will be made by a review committee, comprised of the study Investigators and Sponsor representatives, who will review the available safety and other relevant data to inform the decision on escalating to a higher dose level (see Section 4.1.1). Refer to the Data Safety Review Charter (DSRC) for further details.
"Number of Patients Planned:	For each dosing schedule, 3 to 6 patients are to be enrolled in each dose-escalation cohort in Part 1a. Up to 60 patients in total are to be enrolled in the dose-escalation cohorts. Six to 12 patients in each expansion cohort (up to 4 cohorts) are to be enrolled in Part 1b.
Diagnosis and Main Criteria for Inclusion:	**Patients meeting all the following criteria will be considered eligible for study entry:** 1) 18 years old or older. 2) Population by study stage: a. Part 1a: Patients with advanced, metastatic, and/or progressive solid tumors for whom there is no effective standard therapy available. b. Part 1b: Patients with histologically confirmed, advanced, metastatic, unresectable, and/or progressive solid tumors for whom there is no effective standard therapy available and their PI3K or deoxyribonucleic acid-protein kinase (DNA-PK)

pathway is deregulated or their tumor genetic profile has been shown to correlate with sensitivity to PI3K and/or DNA-PK inhibition based on clinical and preclinical experience. Specific criteria will be determined based on ongoing experiments and will be introduced in a future protocol amendment.

3) Evaluable or measurable disease.
4) Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
5) Able to take oral medications.
6) If a woman of childbearing potential (WOCBP), the patient has a negative serum or urine pregnancy test within 1 week before Cycle 1, Day 1 (C1D1). Refer to Section 8.1.3 for further practical information about contraception.
7) The patient (either male or female) agrees to use acceptable contraceptive methods for the duration of time in the study, and to continue to use acceptable contraceptive methods for 1 month after the last dose of SL-901. Refer to Section 8.1.3 for further practical information about contraception.
8) Able to provide written informed consent.
9) Willing to provide consent for biomarker analysis of (existing paraffin-embedded) tumor samples.

	Patients meeting any of the following criteria will be excluded from the study: 1) Received an investigational anticancer drug within 4 weeks of the first planned SL-901 dose. 2) Received major surgery, radiotherapy, or immunotherapy within 4 weeks of C1D1. Localized palliative radiotherapy is permitted for symptom control. 3) Received chemotherapy regimens with delayed toxicity within 4 weeks (6 weeks for prior nitrosourea or mitomycin C) of C1D1. 4) Received chemotherapy regimens given continuously or on a weekly basis which have limited potential for delayed toxicity within 2 weeks of C1D1. 5) Clinically significant, unresolved toxicity from previous anticancer therapy ≥Grade 2 (except alopecia), as determined by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. 6) Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of drugs. 7) Left ventricular ejection fraction <50%. 8) Corrected QT interval (based on Fridericia's formula) >450 msec. 9) Type 1 or 2 diabetes mellitus requiring medication. (In Part 1b, patients with type 2 diabetes mellitus controlled by medication, as indicated by a glycated hemoglobin of ≤7.5% are eligible.) 10) Known active human immunodeficiency virus, hepatitis B, or hepatitis C infection. 11) Ongoing systemic bacterial, fungal, or viral infection. 12) History of interstitial pneumonitis. 13) Absolute neutrophil count (ANC) <1.5×10^9/L. 14) Hemoglobin <10 g/dL. 15) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of normal (ULN). 16) Known hypersensitivity or allergy to the active ingredient or excipients of SL-901. 17) Breast-feeding females.
Test Products, Doses, and Mode of Administration:	In Part 1a, the SL-901 starting dose on the 20 mg on both the QD and BID schedule. Dose levels planned to be tested in both QD and BID schedules will be tested in parallel, with enrollment to the current cohort for each schedule conducted on an every other patient basis (see Table 5). A treatment cycle is 28 days, with daily dosing throughout the cycle. The regimen of SL-901 for Part 1b of the study will be based on the clinical experience from Part 1a.
Duration of Treatment:	Patients whose disease has not progressed and who have not discontinued due to toxicity, may continue to receive additional cycles of SL-901 at the same dose and schedule.

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Safety:	Patients' medical history will be collected during Screening and updated prior to the first SL-901 dose. Safety assessments include physical examinations, safety laboratories (clinical chemistry, hematology, and coagulation), vital signs and weight, ECOG performance status, and electrocardiograms (ECGs) (performed according to the schedule in Table 8). Assessment of AEs and concomitant medications will be performed for each patient throughout the study. An End-of-Treatment (EOT) visit to include safety laboratory evaluation plus adverse events and concomitant medication checks, will be conducted 30 days after the last dose of SL-901.
Efficacy:	Tumor assessment by will occur at Screening (for identification of baseline disease) and after every 2 cycles of treatment thereafter. Response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer 2009). After completion of the EOT visit, patients will then be followed every 90 days for survival status for 12 months. The survival follow-up may be by telephone contact. If the patient discontinued study drug for reasons other than progressive disease, disease assessments should continue to be performed on an every 8-week basis (±1 week) through 6 months after the first study drug dose and then on an every 90-day basis or until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease.
Statistical Methods:	Study data will be reviewed in accordance with the Statistical Analysis Plan described in Section 9.3.

1.2. Schedule of Assessments

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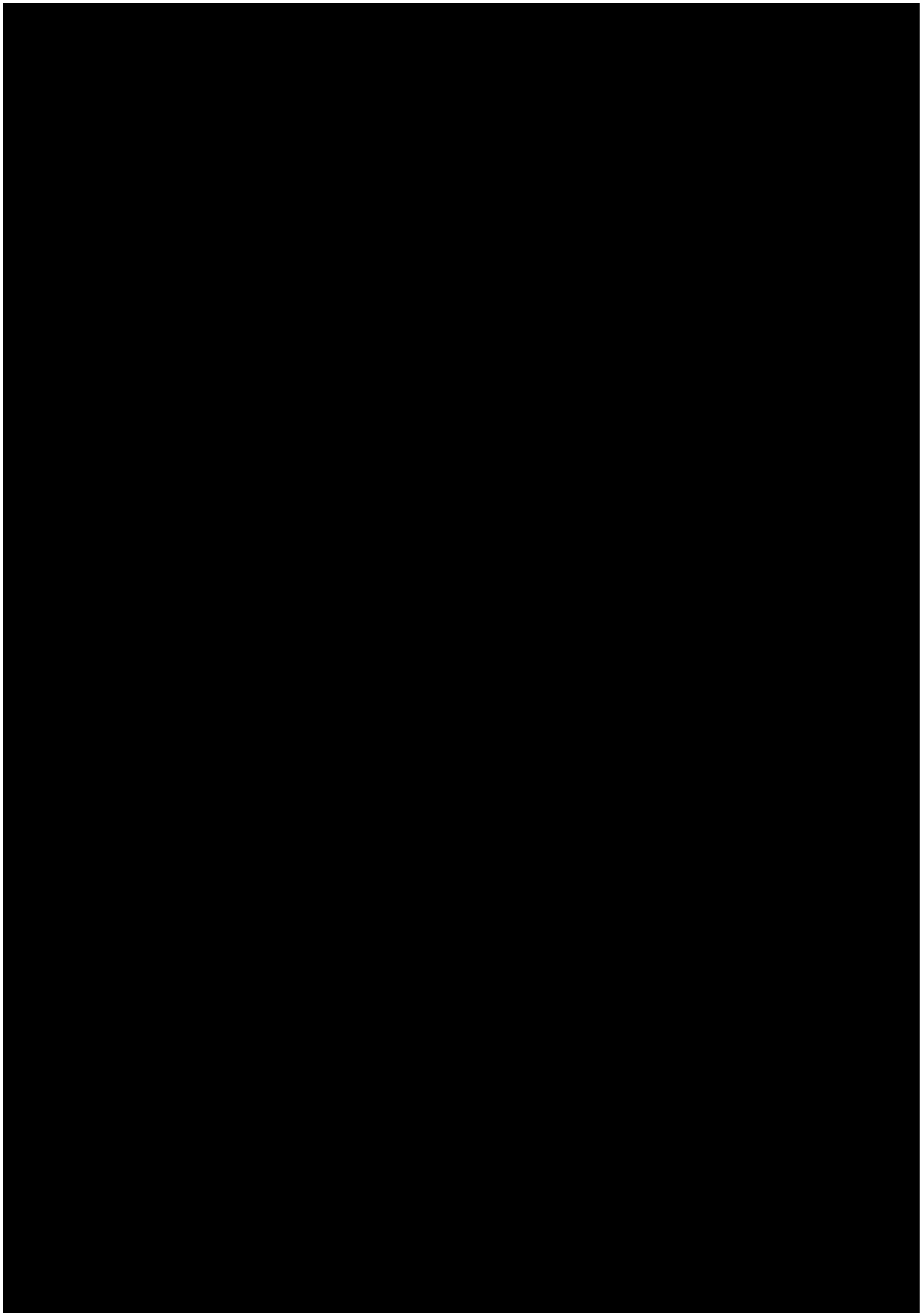
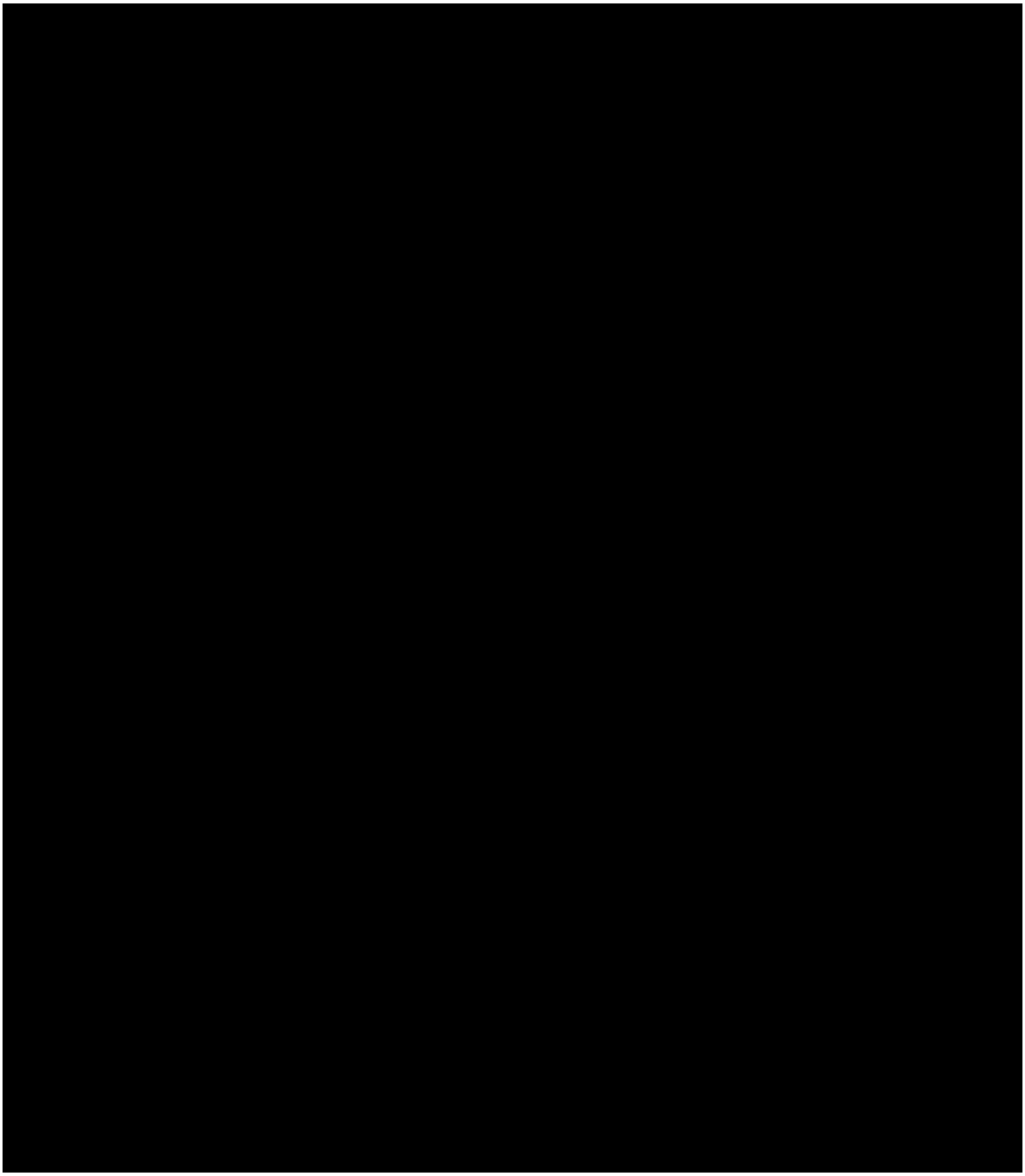




2. INTRODUCTION

2.1. Background

2.1.1. Phosphoinositide 3-Kinases (PI3K) as a Cancer Target

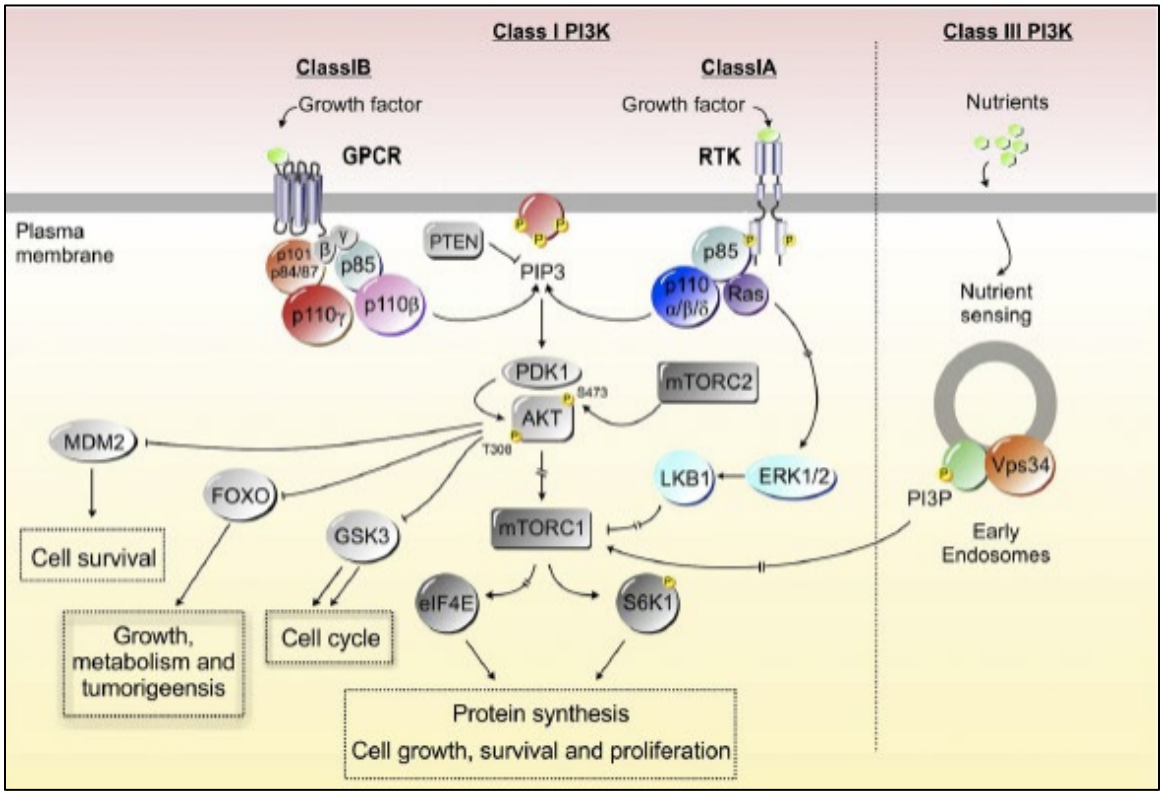
PI3K enzymes are a family of lipid kinases that phosphorylate the 3-hydroxyl group of the inositol ring of phosphoinositols. The most important product of this process is phosphatidylinositol-3,4,5- triphosphate, that serves as a secondary messenger that triggers fundamental cellular processes such as cell growth, survival, motility and metabolism. PI3K isoforms phosphorylate phosphatidylinositol diphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3), which is a secondary messenger that triggers the activation of other downstream kinases such as RAC-α serine/threonine-protein kinase (AKT), glycogen synthase kinase 3 (GSK3)-β and mammalian target of rapamycin (mTOR) (see Figure 1). Dysregulated PI3K signaling in cancers is typically manifested as constitutive signaling of the pathway, either because of mutated upstream membrane receptors, gain of function mutations in the PI3K gene, or loss of function mutations in the gene encoding the phosphatase and tensin homolog (PTEN) phosphatase, which acts as a negative-regulator of the signaling pathway by removing a critical phosphate from the inositol moiety of PIP3, thereby inhibiting the signaling cascade downstream of PIP3 (Courtney 2010).

The importance of the PI3K pathway for tumorigenesis is evidenced by the high frequency of overactive PI3K signaling in a variety of malignancies from different tissues of origin (Liu 2009):

- Critical point mutations in the PIK3CA gene, encoding for the p110-α catalytic subunit of PI3K-α, were commonly found in breast (27%), endometrial (24%), urinary tract (17%), colon (15%), and upper digestive tract (11%) cancers, and in 2% to 9% of skin, stomach, ovaries, liver, brain, oesophagus, prostate and thyroid cancers.
- Amplification of the PIK3CA gene was commonly found in cervical (69%), gastric (36%) and head and neck (32%) tumors; this amplification was also commonly observed in different sub-types of lung cancers, including squamous cell (53%), small cell (21%), adeno (13%) and non-small cell (12%) carcinomas. In cancers of the ovaries, endometrium, breast, cervix, thyroid, astrocytes and oesophagus the frequencies of amplified PIK3CA ranged from 6% to 12%.
- Loss of heterozygosity of the PTEN-encoding gene occurred in 25% to 37% of cancers of the skin, prostate, brain, stomach and breast. Loss of function mutations were observed in cancers of the vulva (65%), endometrium (38%), brain (21%), skin (17%), and prostate (14%).

Targeting PI3K also represents a rational therapeutic approach in cancers with overactive PI3K signaling due to abnormal activity of an upstream receptor tyrosine kinase (RTK) or G protein coupled receptors (GPCR) signaling pathway. Mutations in Ras-encoding genes can also lead to overactive signaling through the PI3K pathway, and therefore PI3K inhibition may also play a role in combination therapies aimed at shutting down alternate signal transduction pathways such as the RAS/BRAF/MEK/ERK pathways.

Figure 1: PI3K/AKT/mTOR Signaling Pathway Schema



(Extracted from: De Santis)

2.1.2. SL-901

SL-901 is an orally bioavailable investigational anticancer drug aimed to treat patients whose cancers harbor an overactive PI3K signaling. SL-901 can also be used in combination with other anticancer therapies in patients whose tumor resistance mechanisms to other therapies rely on signaling through the PI3K pathway, even when PI3K is not mutated.

SL-901 is a PI3K inhibitor with a 50% inhibitory concentration (IC_{50}) in the nanomolar (nM) range against all 4 isoforms of PI3K; however, its IC_{50} against the α and δ isoforms is approximately one order of magnitude lower than against the β and γ isoforms (the SL-901 IC_{50} values against PI3Kα and PI3Kδ are 4.6 and 2.4 nM, respectively). SL-901 also inhibits PI3KC2β and deoxyribonucleic acid-dependent protein kinase (DNA-PK), with an IC_{50} of 10 and 20 nM, respectively.

2.1.2.1. Nonclinical Experience

[redacted]

[redacted]

2.1.2.2. Clinical Experience

A Phase 1 first-in-human dose-escalation study of single-agent SL-901 administered QD in 21-day cycles until development of unacceptable toxicity or progressive disease had enrolled 13 patients in 4 cohorts (5 mg/day [N=4]; 10 mg/day [N=3]; 20 mg/day [N=3] and 40 mg/day [N=3]), before the termination of the study by the prior Sponsor. While only limited clinical data are available from this study, no dose-limiting toxicities (DLTs) occurred at doses up to 40 mg/day. Furthermore, no deaths or SL-901-related serious adverse events (SAEs) or ≥Grade 3 treatment-emergent adverse events (TEAEs) were reported. No efficacy analysis was performed in the study.

2.2. Rationale for Current Study and Risk/Benefit Assessment

SL-901 is an orally bioavailable adenosine triphosphate (ATP) homologue-type, competitive, kinase inhibitor that competes with ATP for binding the ATP-binding pocket of the catalytic subunit of PI3K enzymes. SL-901 induces cell cycle arrest in the G1/0 phase of the cell cycle, and therefore is considered cytostatic rather than cytotoxic or apoptosis-inducing. SL-901 IC_{50} against the α and δ isoforms is approximately one order of magnitude lower than against the β and γ isoforms. The SL-901 target profile partially overlaps with the profile of PI3Kα inhibitors that demonstrated clinical activity in solid tumors and PI3Kδ inhibitors that demonstrated activity in lymphomas.

SL-901 may have a different therapeutic window than the currently available PI3K inhibitors, as it is a more potent inhibitor of the PI3Kα and PI3Kδ isoforms than of the PI3Kβ and PI3Kγ isoforms, and also inhibits PI3KC2β and DNA-PK with an IC_{50} of 10 and 20 nM, respectively, a profile that is different from those seen in currently available PI3K inhibitors (see Table 3).

Table 3: Summary of IC_{50} Values and Targets for Approved PI3K Inhibitors and SL-901

3. OBJECTIVES AND ENDPOINTS

This is a two-part study:

- In Part 1a, escalating doses and 2 schedules (QD and twice daily [BID]) of SL-901 administered daily in a 28-day treatment cycle will be evaluated in patients with advanced solid tumors, to identify the maximum tolerated dose (MTD) and determine the regimen for Part 1b.
- In Part 1b, the safety of the selected administration regimen of SL-901 will be assessed, as well as an initial assessment of clinical activity in patients with advanced solid tumors known to have specific genetic alterations that may derive benefit from treatment with a PI3K inhibitor.

The study objectives and endpoints are summarized in Table 4.

Table 4: Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• To identify the MTD of SL-901. • To identify an appropriate dosing regimen for further investigation of SL-901. • To characterize the PK profile of SL-901. • To generate clinical safety data and perform initial assessment of the safety profile of SL-901.	• Safety endpoints include identification of DLTs; rate of TEAEs and SAEs; identification of abnormalities in physical examination, vital signs, clinical laboratory evaluations, and ECG findings. • PK endpoints include assessment of SL-901 plasma concentration over time; assessment of any changes in the PK properties of SL-901 between initial administration and steady-state and between cycles of treatment; explore the correlation between PK parameters and toxicity.
Secondary	
• To characterize the PD of SL-901. • To assess preliminary clinical activity of SL-901.	• PD assessment of target phosphorylation will be performed using a PI3K pathway triple assay (p-AKT, p-p70S6K, and p-GSK3) in platelet-rich plasma and/or tumor tissue and using immunofluorescence for gamma H2AX in PBMCs. • Clinical activity endpoints include the rate of objective response, rate of CR, DOR, PFS, and OS.

CR = complete response, DLT = dose-limiting toxicity, DOR = duration of response, ECG = electrocardiogram, MTD = maximum tolerated dose, OS = overall survival, p-AKT = phosphorylated-RAC-alpha serine/threonine-protein kinase (protein kinase B), p-GSK3 = phosphorylated glycogen synthase kinase 3, p-p70S6K = phosphorylated p70S6 kinase, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamic(s), PFS = progression-free survival, PI3K = phosphoinositide 3-kinase, PK = pharmacokinetic(s), SAE = serious adverse event, TEAE = treatment-emergent adverse event

4. STUDY DESIGN

4.1. Overall Design and Operational Characteristics

This clinical study includes 2 parts:

1) Part 1a: an open-label, dose-escalation, and regimen-finding study to investigate the safety, PK, and PD of SL-901 in patients with advanced solid tumors. In Part 1a, adverse events (AEs) occurring during the first cycle of treatment will be considered for the assessment of DLTs, with continued evaluation of AEs in subsequent treatment cycles for further characterization of the safety of SL-901. This part will follow a 3+3 dose-escalation design to determine the MTD of SL-901 when administered on both a QD and BID schedule; single and multiple dose PK assessments will be performed to characterize the exposure of SL-901. The dose-escalation scheme to be followed is based on a modified Fibonacci sequence schema, which also is commonly employed in Phase 1 dose-finding oncology studies (Storer 1989).
2) Part 1b: Up to 4 expansion cohorts of patients with specific genetic alterations that may derive benefit from treatment with a PI3K inhibitor will be treated SL-901 with the dose regimen selected in Part 1a.

This clinical study will explore different dose levels and schedules of SL-901 given as a single agent, therefore the term “regimen” is comprised of the unit dose administered and the specified schedule of dosing in a given cohort.

4.1.1. Dose-Escalation (Part 1a)

Part 1a employs a standard 3+3 design. The SL-901 starting dose will be 20 mg on both the QD and BID schedule. The QD and BID schedules are planned to be tested in parallel, with enrollment to the current cohort for each schedule conducted on an every other patient basis. A treatment cycle is 28 days, with daily dosing throughout the cycle. The planned dose levels are summarized in Table 5.

Table 5: Planned SL-901 Dose Levels in Part 1a

	Cohort						
	1	**2**	**3**	**4**	**5**	**6**	**7**
QD Dosing (mg/dose)	20	40	60	80	120	160	200
BID Dosing (mg/dose)	--	20	--	40	60	80	100
Total Daily Dose (mg/day)	20	40	60	80	120	160	200

QD = once daily, BID = twice daily

4.1.2. Expansion Cohorts (Part 1b)

Up to 4 expansion cohorts at the MTD (or maximum tested dose if no MTD is identified, or dose below the MTD if there is evidence suggesting a more favorable risk/benefit profile) may be opened for enrollment with 6 to 12 patients in each cohort.

Although decisions regarding dose-escalation will be made based on review of data from Part 1a, safety data will also be collected from all patients in Part 1b and reviewed

periodically by the Sponsor and Investigators. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, including further refinement of the MTD.

4.1.3. Justification for Study Design

Goals of Phase 1 oncology studies include estimation of the initial safety and tolerability of a study drug, establishment of an MTD, determination of a recommended range of doses for evaluation in future clinical studies (Ahn 1998, Gastontis 1992, International Conference on Harmonisation 1997), and an initial characterization of the PK profile in humans. The objectives of the current study are consistent with those typical of Phase 1 oncology studies.

Preliminary assessment of activity or potential therapeutic benefit may be a secondary objective of Phase 1 studies (International Conference on Harmonisation 1997). Consistent with this premise, a secondary objective is to evaluate the potential anti-tumor activity of SL-901.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients meeting all the following criteria will be considered eligible for study entry:

1. 18 years old or older.
2. Population by study stage:
    a. Part 1a: Patients with advanced, metastatic, and/or progressive solid tumors for whom there is no effective standard therapy available.
    b. Part 1b: Patients with histologically confirmed, advanced, metastatic, unresectable, and/or progressive solid tumors for whom there is no effective standard therapy available and their PI3K or DNA-PK pathway is deregulated or their tumor genetic profile has been shown to correlate with sensitivity to PI3K and/or DNA-PK inhibition based on clinical and preclinical experience. Specific criteria will be determined based on ongoing experiments and will be introduced in a future protocol amendment.
3. Evaluable or measurable disease.
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
5. Able to take oral medications.
6. If a woman of childbearing potential (WOCBP), the patient has a negative serum or urine pregnancy test within 1 week before Cycle 1, Day 1 (C1D1). Refer to Section 8.1.3 for further practical information about contraception.
7. The patient (either male or female) agrees to use acceptable contraceptive methods for the duration of time in the study, and to continue to use acceptable contraceptive methods for 1 month after the last dose of SL-901. Refer to Section 8.1.3 for further practical information about contraception.
8. Able to provide written informed consent.
9. Willing to provide consent for biomarker analysis of existing paraffin-embedded tumor samples.

5.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Received an investigational anticancer drug within 4 weeks of the first planned SL-901 dose.
2. Received major surgery, radiotherapy, or immunotherapy within 4 weeks of C1D1. Localized palliative radiotherapy is permitted for symptom control.
3. Received chemotherapy regimens with delayed toxicity within 4 weeks (6 weeks for prior nitrosourea or mitomycin C) of C1D1.
4. Received chemotherapy regimens given continuously or on a weekly basis which have limited potential for delayed toxicity within 2 weeks of C1D1.

5. Clinically significant, unresolved toxicity from previous anticancer therapy ≥Grade 2 (except alopecia), as determined by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.
6. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of drugs.
7. Left ventricular ejection fraction <50%.
8. Corrected QT interval (based on Fridericia's formula) >450 msec.
9. Type 1 or 2 diabetes mellitus requiring medication. (In Part 1b, patients with type 2 diabetes mellitus controlled by medication, as indicated by a glycated hemoglobin of ≤7.5% are eligible.)
10. Known active human immunodeficiency virus, hepatitis B, or hepatitis C infection.
11. Ongoing systemic bacterial, fungal, or viral infection.
12. History of interstitial pneumonitis.
13. Absolute neutrophil count (ANC) $<1.5\times10^9$/L.
14. Hemoglobin <10 g/dL.
15. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of normal (ULN).
16. Known hypersensitivity or allergy to the active ingredient or excipients of SL-901.
17. Breast-feeding females.

5.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently treated with SL-901. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. The required information includes demography, screen failure details, eligibility criteria, and any SAE experienced.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once. Rescreened patients will be assigned a new patient number (different from the initial Screening number).

5.4. Source of Patients

This will be a multi-center study. Each study center is required to obtain local Institutional Review Board (IRB)/Ethics Committee (EC) and national regulatory approval to conduct the study before enrollment of patients may commence. Patients meeting the entrance criteria who are known or referred to the study center will be eligible for enrollment.

6. STUDY DRUG

6.1. Study Drug Supply

All patients participating in this study will receive SL-901 as a single agent in an open-label fashion. The Sponsor will supply SL-901 to all clinical sites.

6.2. Study Drug Packaging and Storage

SL-901 capsules (20 mg and 60 mg) are packaged into 50-cc high-density polyethylene (HDPE) bottles, 14 capsules per bottle. Bottles are capped with a child resistant tamper evident polypropylene closure.

All bottles are labeled with a single panel clinical label containing pertinent information for drug receipt and handling. Labeled bottles of 20 mg and 60 mg SL-901 capsules received from the distributor should be stored in a locked cabinet accessible only to appropriate study personnel.

SL-901 capsules are not to be stored above 25°C or frozen and are to be stored protected from light. Keep out of reach of children. For additional information on study drug handling including dispensing directions refer to the SL-901 Pharmacy Manual.

6.3. Study Drug Accountability

Study drug will be dispensed to patients at scheduled study center visits on a per-cycle basis. The Investigator or designee will maintain accurate records of receipt and condition of the study drug, including dates of receipt and temperature monitoring. In addition, records will be kept of the date dispensed, quantity dispensed, and the patient to whom study drug was dispensed. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded in source documents and in the electronic case report form (eCRF).

The Investigator or designee is responsible for the accountability of all used and unused study drug containers and unused study drug. The site identification number and patient identification number are to be recorded on each study drug accountability log. Each time study personnel dispenses study drug for a patient, he or she is to record the date dispensed, number of capsules of study drug dispensed, and his or her initials. When the patient returns study drug, study personnel are to record the date returned, the number of capsules returned or empty bottle(s), and any comments. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused containers. The Clinical Research Associate (CRA) will review study drug accountability records during routine monitoring visits. At the completion of the study, there will be a final reconciliation of all study drug.

6.4. SL-901 Dose and Administration

In both study parts, for the purposes of this study, a treatment cycle is considered to be 28 days, with daily dosing throughout the cycle.

Each SL-901 dose will be self-administered by the patient without food, either 2 hours before or 2 hours after food. The dose regimen is dependent on the patient's cohort assignment (see Table 5), and SL-901 doses should be administered at approximately the same time of day on each day of the cycle, if possible. For patients on the BID schedule, doses should be taken morning and evening at approximately the same time each day of the cycle, if possible.

On PK sample collection days, SL-901 should be administered at the study center and should be administered at (approximately) the same time of day on each day of the cycle, if possible. For patients on the BID schedule, start of PK collection must occur before the first dose of the day.

In Part 1a, the SL-901 starting dose is 20 mg on a QD schedule and a total daily dose of 40 mg on a BID schedule, as specified in Table 5. The QD and BID schedules will be tested in parallel, with enrollment to the current cohort for each schedule conducted on an every other patient basis.

In Part 1b, the regimen of SL-901 will be based on the clinical experience in Part 1a.

6.4.1. Dose-Escalation Scheme in Part 1a

Initially, up to 3 patients are to be enrolled in each cohort. After 3 patients complete C1 and have safety evaluations performed through C2D1, and if:

- None of these 3 patients experience a DLT in either dosing schedule, then enrollment of the next cohort may commence.
- 1 of 3 patients within a cohort experiences a DLT, then up to 3 additional patients are to be enrolled sequentially at that dose level in that dosing schedule. If none of the additional 3 patients experience a DLT (i.e., 1 of 6 patients has a DLT), then enrollment at the next scheduled dose may commence.
- ≥2 patients within a cohort experience a DLT, then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD for that dosing schedule.

Note that enrollment in the next dose cohort can begin only when the last patient enrolled in the current dose cohort completes C1 and is assessed for DLT, provided that <2 patients in the current dose cohort experienced a DLT.

Although decisions regarding dose-escalation will be made based on review of data from C1, safety data will also be collected from all patients continuing treatment and this will be reviewed periodically. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, including further refinement of the MTD.

Based on evaluation of the safety and tolerability data, it may be decided that escalation to the next dose level should be more conservative than specified and that the next higher dose will be an intermediate dose level.

An MTD will be identified for each dosing schedule.

6.4.2. Dose-Limiting Toxicities

Patients are to receive at least 75% of the planned SL-901 doses in C1 and complete study assessments through C2D1 to be eligible for DLT evaluation, unless discontinuing due to DLT. Patients who receive <75% of the planned SL-901 doses in C1 and/or discontinue before completing study assessments through C2D1 for reasons other than DLT are to be replaced.

Toxicities are to be assessed by the Investigator according the NCI CTCAE, v5.0 (available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

A DLT occurring during the Run-in PK period or in C1 is defined as any of the following AEs for which there is a reasonable possibility that SL-901 caused the event. (Note that while causality of an AE is to be determined by the Investigator, the Sponsor's assessment of causality can be used to override an Investigator's designation of 'unrelated'; however, the Sponsor's assessment cannot be used to reverse an Investigator's designation of 'related' for the purpose of DLT determination.

- Any ≥Grade 3 non-hematologic AEs, with the exceptions of:
  - Grade 3 nausea, vomiting, diarrhea, constipation, fever, fatigue, or skin rash that resolves to Grade <3 within 72 hours.
  - Grade 3 laboratory abnormalities that are not associated with symptoms and resolve to Grade 1 or baseline by C1D28 (unless otherwise specified).
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with >Grade 1 bleeding or requirement for platelet transfusion.
- Grade 4 neutropenia lasting >5 days.
- Febrile neutropenia (ANC $<1\times10^9$/L with fever ≥38.5°C) of any duration.
- Persistent anemia (i.e., lasting >96 hours despite >2 red blood cell [RBC] transfusions).
- ≥Grade 3 transaminase (AST/ ALT) elevation.
- Any toxicity resulting in >7 held/skipped doses.
- Any other significant toxicity considered by the Investigator or the Sponsor to be dose-limiting (e.g., any toxicity considered at least possibly related to SL-901 that results in patient withdrawal during C1).

In situations in which DLTs have occurred that would prevent further dose-escalation and are severe but not life-threatening (i.e., persistent Grade 3 fever, malaise), re-evaluation of specific dose cohorts may be considered with co-administration of appropriate supportive care agents (e.g., corticosteroids, anti-depressants) concomitant with SL-901 therapy.

6.4.3. Operational Characteristics of Dose-Escalation

All dose-escalation steps and schedule recommendations will be made by a review committee, comprised of the study Investigators and Sponsor representatives, who will review the available safety and other relevant data to inform the decision. Refer to the Data Safety Review Charter (DSRC) for further details.

A sample size of at least 3 patients in each cohort, expanding to 6 patients in the event of a marginal DLT rate (33%), is a conventional approach in dose-escalation studies of investigational oncologic agents.

6.5. Rationale for the Dose(s) Selected

6.6. Dose Interruptions and Reductions

For patients that develop a clinically significant AE or unacceptable toxicity during treatment, dosing should be interrupted.

- If the toxicity resolves to the baseline level or Grade 1 within 7 days, then dosing should resume at the same dose level (during C2 and beyond, dose reduction may also be considered in consultation with the Sponsor).
- If the toxicity resolves to the baseline level or Grade 1 within 8 to 14 days, then dosing in C2 and beyond may be resumed at a reduced dose after consultation with the Sponsor.
- If the toxicity fails to resolve to baseline or Grade 1 within 14 days, then the patient should be discontinued from treatment permanently.

Specific management of unusual non-autoimmune and non-infectious toxicities known to be associated with PI3K inhibitors are summarized in Table 6 (Greenwell 2017).

Table 6: Management of Unusual Non-Autoimmune and Non-Infectious Toxicities

	Hypertension	**Hyperglycemia**	**Confusion**	**Anxiety/ depression**	**Rash**
Observe	BP ≥ 140/90 mmHg	FG ULN-160 mg/dL	Mild disorientation	Mild symptoms	≤30% BSA
Hold Drug	BP ≥ 200/110 mmHg	FG >160 mg/dL or NFG ≥200 mg/dL	Limit ADL	Limit ADL	>30% BSA

Abbreviations: ADL = activities of daily living, BP = blood pressure, BSA = body surface area, FG = fasting glucose, NFG = non fasting glucose, ULN = upper limit of normal

6.6.1. Intra-Patient Dose-Escalation

Intra-patient dose escalation to the MTD may be considered for patients who, at the time the MTD is determined, have experienced a confirmed objective response or stable disease for at least 4 treatment cycles with SL-901; AND have not experienced any ≥Grade 3 toxicity that was considered by the Investigator to be related to SL-901; AND do not exhibit any evidence of cumulative toxicity that can be considered related to SL-901.

7. STUDY INTERVENTION DISCONTINUATION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Patient Withdrawal and Replacement

Patients may be withdrawn from the study for any of the following reasons:

- Patient, Investigator, or Sponsor request.
- Protocol violation.
- Non-compliance to protocol.
- AE.
- Pregnancy.
- Progression of disease that, in the opinion of the Investigator, precludes further study treatment.
- Lost to follow-up.

The reason for study withdrawal is to be documented in the patient's source documents and eCRF.

See Section 6.4.2 for replacement of patients that discontinue treatment during C1. Patients that discontinue treatment after C1, for any reason and at any stage, will not be replaced.

7.2. Dose Modifications

In Part 1a, dose modifications are not allowed in the PK Run-in Period and C1.

7.3. Treatment Discontinuation

Study drug may be discontinued for any of the following reasons:

- Progression of disease that, in the opinion of the Investigator, precludes further study treatment. After consultation with the Sponsor, SL-901 may be continued for a patient who has met the criteria for progressive disease but in the Investigator's opinion, continues to derive benefit from study treatment.
- Occurrence of an unacceptable AE, including DLT.
- Pregnancy.
- SL-901 interruption due to study drug-related toxicity for >1 cycle (i.e., >28 days). Interruptions or delays >28 days for reasons other than AEs and/or in the setting of sustained disease control may be acceptable and are to be discussed with the Medical Monitor.
- Patient requires use of a prohibited concomitant medication or therapy.
- General or specific changes in the patient's condition unacceptable for further treatment within the study parameters, in the judgment of the Investigator.
- Non-compliance.

- Lost to follow-up.
- Patient withdrawal of consent.
- Sponsor request.
- Other.

All study procedures outlined for the End-of-Treatment (EOT) visit should be performed 30 days (±3 days) after the last study drug dose.

In Part 1a, patients who receive <75% of the planned SL-901 doses in C1 and/or discontinue from the study before completing study assessments through C2D1 for reasons other than DLT are to be replaced.

7.4. Lost to Follow-Up

A patient will be considered lost to follow-up if they are unable to be contacted by the study site staff.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site will attempt to contact the patient and reschedule the missed visit within 7 days of the originally planned study visit and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the patient. These contact attempts should be documented in the source documents, and at least three documented contacts are needed to consider a patient lost to follow-up.

Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS

8.1. Screening Assessments

Screening assessments are performed subsequent to the patient providing an informed consent and before the first administration of SL-901 at the Run-in PK sampling day, see Section 8.7. These assessments are to be performed within 28 days of the Run-in PK sampling day (during Screening), unless otherwise specified.

8.1.1. Demographic Data, Medical History, ECOG Performance Status, and Cancer History

Patient demographics, including age, sex, race, and ethnicity, are to be documented during Screening.

The medical history is to include cancer history, including the patient's primary tumor type, current disease stage, date of and disease stage at diagnosis, and all previous treatments, including systemic therapy, radiation therapy, and surgeries, as well as response to such treatment, when available.

A complete medical history is to be documented during Screening. The medical history should include a minimum of the prior 2 years, whenever possible, with information for longer durations, when feasible. ECOG performance status also is to be documented during Screening.

8.1.2. Prior Medications

All medications taken within 28 days before the initial Screening visit through the EOT visit, including nonprescription medications, dietary supplements and the specific dose/schedule of any systemic corticosteroid agents, should be recorded.

8.1.3. Contraception, Pregnancy and Pregnancy Testing

From the time of provision of written informed consent throughout the duration of the study, and for 1 month after last dose of SL-901, female subjects of childbearing potential must use a highly effective method of contraception. This also applies to any female partners of male study participants.

Serum or urine samples for beta-human chorionic gonadotropin pregnancy testing are to be collected from WOCBP during Screening to be eligible for participation in the study. A pregnancy test must be collected during the Run-in visit and this pregnancy test result must be reviewed and determined to be negative before administration of the first study drug dose at the Run-in PK sampling visit. Pregnancy testing is to be repeated monthly at the Day 1 visit of each cycle beginning with Cycle 2 and again after the last SL-901 dose, (at a time after the end of the relevant period of exposure). Pregnancy testing during the study should additionally occur at any time pregnancy is suspected.

A WOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months; or women on hormone replacement therapy with documented serum follicle-stimulating hormone level ≥35 mIU/mL).

A highly effective method of contraception is defined as one that has no higher than a 1% failure rate. In this study, the only highly effective methods of contraception are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, including oral, intravaginal, and transdermal formulations.
- Progestogen-only hormonal contraception associated with inhibition of ovulation, including oral, injectable, and implantable formulations.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner, provided that partner is the sole sexual partner of a study patient of child-bearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence, when this is in line with the preferred and usual lifestyle of the study patient. (Periodic abstinence [.eg, calendar, ovulation, symptothermal, post ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

Male patients in this study must consent to use a condom throughout the duration of the study, and for 1 month after last dose of SL-901, and their female partners who are of child-bearing potential must use highly effective contraception, as listed above.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. This information will be included in the informed consent form (ICF) that must be signed by the patient. In addition, all WOCBP or fertile men with partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Patients with a positive pregnancy test result during Screening are not eligible for study participation. Patients with a positive result at any time after the start of study drug administration are to have study drug permanently discontinued. Refer to Section 8.6 for details regarding management of any pregnancies during the study.

8.1.4. Physical Examination

A complete physical examination, including measurement of height, is to be performed during Screening, on Day 1 of each cycle and at End of Treatment. Physical examinations are to be conducted by a physician or health professional licensed to perform physical

examinations and designated by the Investigator. The complete physical examinations should include assessment of the following:

- General appearance
- Eyes, ears, nose, and throat
- Head and neck
- Chest and lungs
- Cardiovascular system
- Gastrointestinal system (abdomen)
- Musculoskeletal system
- Lymphatic system
- Dermatologic
- Neurological (including questioning regarding whether the patient is experiencing any numbness and/or pain as well as light touch, sharp touch [skin prick], and temperature, position [proprioception], and vibration sensation testing. Additional neurological assessments are to be performed as appropriate for the patient's condition, at the Investigator's discretion.)
- Psychiatric
- Extremities

Symptom-directed (i.e., abbreviated) physical examinations are to be conducted at all other study visits.

Abnormal physical examination findings that are considered by the Investigator to be clinically significant during Screening and before initial dosing are to be reported as part of the patient's medical history. Abnormal, clinically significant examination findings following initiation of dosing are to be reported as AEs, if the finding represents worsening from baseline or new onset.

8.2. Adverse Events and Serious Adverse Events

8.2.1. Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a study patient who is administered a medicinal product (study drug), regardless whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign including abnormal laboratory/examination findings, symptoms, or disease(s) temporally associated with the use of study drug, whether or not related to study drug. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Serious Adverse Event (SAE)

An AE is considered serious (i.e., an SAE) if, in the view of either the Investigator or Sponsor, it meets any of the following criteria:

- Results in death.
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned before study entry are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.

Important Medical Event (IME)

An important medical event (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Note: The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

8.2.2. Adverse Event Assessment and Reporting

All serious and non-SAEs will be recorded in the study's clinical database:

- AEs – from the day of first exposure to SL-901 through 30 days after the last dose of SL-901.
- SAEs – from the day of informed consent signature by the patient through 30 days after the last dose of SL-901.

This includes AEs that patients report spontaneously, those observed by the Investigator, and those elicited by the Investigator during scheduled study center visits.

All AEs entered into the clinical database are to contain the following details regarding the AE: diagnosis/AE term (in case diagnosis is unknown), start/stop date, intensity, relationship to study drug, action taken with study drug due to the event, whether intervention was required, outcome, and whether the event is classified as serious. The Investigator must continue to follow all SAEs and non-serious AEs until resolution, or until the Investigator assesses them as chronic or stable.

Each AE is to be assessed by the Investigator for the following categories.

Serious/Non-Serious

AEs that meet the criteria specified in Section 8.2.1 are to be considered serious.

Relationship to Study Drug

The relationship of each AE to study drug is to be assessed by the Investigator according to the following criteria:

- Related: A temporal relationship exists between the event onset and administration of SL-901. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. This includes events that are considered possibly, probably, or definitely related to SL-901.
- Not Related: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered probably not or not related to SL-901. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting (in other words, disease progression is not considered an AE; however some sequelae of disease progression may be reported as AEs and should generally be reported as AEs not related to investigational therapy).

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. The following factors for study drug relationship should be referenced when making a determination of "related" or "not related."

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication: The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug: the known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Intensity

The intensity of each AE is to be assessed by the Investigator according to the NCI CTCAE Version 5.0 (available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). If the AE is not included in the NCI CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

Mild (Grade 1): AE that disappears or is easily tolerated on continuation of study drug.

Moderate (Grade 2): AE that disappears or is easily tolerated on continuation of study drug.

Severe (Grade 3): AE sufficiently discomforting to cause interference with usual work activities.

Life-Threatening (Grade 4): AE that is *potentially* life-threatening.

Death (Grade 5): Results in the patient's death.

A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events as previously defined.

8.2.3. Reporting Serious Adverse Events

The Investigator must report all SAEs within 24 hours of discovery via e-mail to the Sponsor's Safety Vendor at the following e-mail:

STML-901-0119_PV@tigermed.net

The completed SAE report is to be sent within 24 hours of discovering the event. The initial report should include at least the following information:

- Patient's study identification number
- Date, description and time (if available) of the event
- Criterion for seriousness
- Preliminary assignment of relationship to study drug

The Safety Vendor will confirm receipt of the report. The Sponsor will review the report and determine if any follow-up queries are needed for the study site. The Investigator will be contacted for follow-up information regarding the SAE, as appropriate. Follow-up reports should be sent in a timely fashion as information becomes available.

SAEs that are considered at least possibly related to the investigational product and unexpected (i.e., Suspected Unexpected Serious Adverse Reactions [SUSARs]), will be

reported to the applicable regulatory authorities and IRB/EC by the Sponsor or Sponsor's designee as required by applicable local regulations. Per regulation, any fatal or life-threatening SUSAR will be reported to the regulatory authorities and IRB/EC within 7 calendar days, and additional information within an additional 8 calendar days. The Sponsor or Sponsor's designee is required to submit any other SUSAR to the regulatory authorities and IRBs/ECs within 15 calendar days of notification. The Sponsor or its designee is also responsible for notifying the investigational sites of all expedited SAEs. The Investigator must keep copies of all expedited SAE information including correspondence with the Sponsor on file.

8.2.4. Special Cases: Overdose and Pregnancy

Overdose is defined as an occurrence in which more drug is administered than the intended amount. Signs and symptoms considered to be a result of an overdose should be reported as AEs. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria (see Section 8.2.1).

Pregnancies or pregnancies of partners by study patients occurring while the patient is receiving SL-901 or within 30 days after the patient's last dose of SL-901 will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 8.2.1 as IMEs.

8.2.5. Protocol Deviations Due to an Emergency or Adverse Event

Generally, deviations from the protocol require pre-approval by the Sponsor on a case-by-case basis. In medical emergency situations, the Investigator or other physician in attendance may exercise their medical judgment without prior approval but will need to subsequently report the deviation to the Sponsor.

8.3. Laboratory Assessments

Laboratory abnormalities that are considered by the Investigator to be clinically significant for a particular patient during Screening and before the first study drug dose are to be reported as part of the patient's medical history. After the first study drug dose, any clinically significant (as determined by the Investigator) worsening in laboratory assessments or other clinical findings should be considered an AE.

Blood samples for hematology and clinical chemistries are to be collected at the time points designated in Table 1 and Table 2.

The laboratory parameters that will be measured during the study are summarized in Table 7.

Table 7: Clinical Laboratory Parameters to be Measured During the Study

Hematology	Hematocrit Hemoglobin Platelet count White blood cell count with differential
Chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bilirubin Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Total protein Uric acid
Coagulation	Prothrombin time or international normalized ratio

8.4. Weight and Vital Signs

Vital signs, including temperature, heart rate, respiration rate, blood pressure (BP), and weight are to be measured. Vital signs should be measured after the patient has been sitting for 3 to 5 minutes.

8.5. Concurrent Medications

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 28 days before the first dose of SL-901 through the EOT visit. On PK sample collection days, both the date and time of concomitant medications and therapies should be recorded.

8.5.1. Prohibited Concurrent Medications

The following medications are prohibited during the study:

- Any investigational agent or device other than SL-901, including agents that are commercially available for indications other than the patient's solid tumor that are under investigation for the treatment of solid tumors.
- Any anti-neoplastic treatment with activity against solid tumors other than SL-901.

8.5.2. Permitted Concurrent Medications

Medications and treatments other than those specified in Section 8.5.1, including palliative and supportive care for disease-related symptoms (e.g., appetite stimulants, stimulants [modafinil], anti-cachexia therapy [fish-oil supplements], anti-depressants, opiate and non-opiate analgesics, antibiotics, selective use of corticosteroids, and, as indicated below, anti-emetic and anti-diarrheal agents and hematopoietic growth factors), are permitted during the study. In case of hyperglycemia grade 3 or higher, treatment with Metformin is permitted.

Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

8.5.3. Additional Important Considerations

Clinical drug-drug interaction studies with SL-901 have not been performed.

Concomitant therapy with drugs that are strong inhibitors or inducers of CYP3A and induce CYP2B6 (e.g., clarithromycin, itraconazole, phenytoin, rifampicin), may cause SL-901 toxicity or lack of efficacy. In addition, drugs that are substrates of CYP3A (e.g., drugs include amlodipine, amitriptyline, and carbamazepine) may reach toxic levels of exposure due to inhibition by SL-901, and therefore caution with use of such drugs is advised.

8.6. Pregnancy

Pregnancies occurring in the patient or patient's partner while the patient is receiving study drug or within 30 days after the patient's last dose of study drug will not be considered serious, but are to be reported as IMEs using the same procedures as for SAEs described in Section 8.2.1.

Study drug must be discontinued immediately in the event of a pregnancy. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy and must notify the Sponsor of the outcome. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported.

8.7. Tumor Assessments

Tumor assessment by will occur at Screening (for identification of baseline disease) and after every 2 cycles of treatment thereafter. Response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer 2009).

After completion of the EOT visit, patients will then be followed every 90 days for survival status for 12 months. The survival follow-up may be by telephone contact. If the patient discontinued study drug for reasons other than progressive disease, disease assessments should continue to be performed on an every 8-week basis (±1 week) through 6 months after the first study drug dose and then on an every 90-day basis or until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease.

8.8. Pharmacokinetics

See Table 8 for the PK assessment schedule.

8.9. Electrocardiogram

Twelve-lead ECGs will be performed 5 to 10 minutes before the PK sample is collected and analyzed locally in triplicate over 5 minutes (±5 minutes) contemporaneously with selected PK sampling time points, as indicated in Table 8.

Table 8: Time Points for Pharmacokinetic and Electrocardiogram Assessments

	Run-in Serial PK Sampling and ECGs (3-7 days before C1D1; Part 1a only)		**Steady State Sampling and ECGs** (C1D8; C1D22; C2D1; C2D8; C2D15; C2D22; Cycles 3 and beyond D1, D15 Part 1a and Part 1b)		**Serial PK Sampling and ECGs** (C1D15 Part 1a and Part 1b)	
Timepoint	**PK**	**ECG[1]**	**PK**	**ECG[1]**	**PK**	**ECG[1]**
Predose	X	X	X	X	X	X
60 minutes postdose	X	X	--	--	X	X
2 hours postdose	X	X	--	--	X	X
4 hours postdose	X	X	--	--	X	--
6 hours postdose	X	--	--	--	X	--
8 hours postdose	X	--	--	--	X	--
10 hours postdose	X	--	--	--	X	--
12 hours postdose	X	--	--	--	X	--
24 hours postdose	X	X	--	--	X	X
48 hours postdose	X	X	--	--	--	--
72 hours postdose	X	X	--	--	--	--

C = cycle, D = day, ECG = electrocardiogram, PK = pharmacokinetic

1. ECG should be performed as triplicates and at least 5-10 minutes before the PK sample is collected.

8.10. Pharmacodynamics

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Basis for Sample Size

No formal sample size calculation is required in this Phase 1 dose-escalation and dose expansion study. For each dosing schedule, 3 to 6 patients are to be enrolled in each dose-escalation cohort in Part 1a. Up to 60 patients in total are to be enrolled in the dose-escalation cohorts.

The total number of patients to be enrolled is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose-escalations required to achieve the MTD.

A sample size of at least 3 patients in each cohort, expanding to 6 patients in the event of a marginal DLT rate (33%), is a conventional approach in dose-escalation studies of investigational oncologic agents.

Six to 12 patients in each expansion cohort (up to 4 cohorts) are to be enrolled in Part 1b.

9.2. Populations for Analysis

The intent-to-treat (ITT) principal will be followed for the safety and efficacy populations. This is defined as all patients enrolled into the study and who received any amount of SL-901.

As warranted by the data, efficacy also may be assessed in a per-protocol population, defined as all patients who receive at least 1 cycle of treatment, have at least 1 post-baseline efficacy assessment, and have no major protocol violations, as defined by the Sponsor.

PK analyses will be performed on the PK population, defined as all patients who receive any amount of SL-901 and have sufficient data for PK analysis.

9.3. Statistical Analysis Plan

9.3.1. Patient Disposition

Data tabulations will summarize the number of patients:

- Enrolled
- At least 1 SL-901 dose received
- Evaluable for safety and efficacy
- Protocol violations
- Withdrawn from study due to:
  - AE
  - Investigator request
  - Withdrew consent
  - Lost to Follow-up
  - Other reasons

9.3.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics of patients will be summarized using descriptive statistics, including:

- Age
- Sex
- Race
- Ethnicity
- Baseline ECOG performance status
- Primary diagnosis
- Disease stage at diagnosis and Baseline
- Prior therapies, including systemic therapies, radiation, and surgeries
- Other baseline characteristics

9.3.3. Concurrent Medications

The number and proportion of patients in the safety analysis set using different concomitant medications will be tabulated and summarized by World Health Organization Drug anatomical, therapeutic, chemical class and preferred term (PT). All concomitant medications administered will be presented in a data listing.

9.3.4. Safety Analyses

Safety analysis will be performed on the ITT population. Safety analyses in addition to those described in the following subsections may be performed at any time without prejudice, in order to most clearly enumerate rates of toxicities and to define further the safety profile of SL-901.

Treatment-Emergent Adverse Events

- AEs will be considered treatment-emergent (i.e., TEAEs) if they start on or after the time of the first dose of SL-901 and up to 30 days after the last dose of SL-901.
- TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™), Version 22 (or higher), system organ class (SOC) and PT. The severity of AEs will also be summarized by NCI CTCAE, Version 5.0 (or higher).
- Non-treatment-emergent AEs will be included in the patient listings and flagged as such but will not be included in the summary tables.
- Where an AE date is partial or missing, and it is unclear whether the AE is treatment-emergent, the AE will be assumed to be treatment-emergent.

Summary of TEAEs

The number and percentage of patients who experience TEAEs will be summarized overall by SOC and PT and will also be summarized based on severity and causality.

Descriptive analysis of AEs will include incidence of TEAEs and SAEs grouped by:

- SOC and PT
- SOC, PT and severity
- SOC, PT and causality
- SOC and PT leading to discontinuation from the study
- SOC and PT for events ≥Grade 3
- SOC and PT leading to death

Individual listings of all AEs will also be provided.

9.3.4.1. Laboratory Parameters

Laboratory results (hematology, chemistry and coagulation parameters) will be graded according to NCI CTCAE, Version 5.0 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Shift tables will generated to display changes from baseline to the worst value on study and last value on study using values provided by the local laboratory.

All laboratory data will be included in listings and abnormal results will be flagged.

9.3.4.2. Vital Signs and Body Weight

Changes in vital sign parameters (including systolic and diastolic blood pressure and heart rate) and body weight will be summarized over time, and any abnormal values will be tabulated.

9.3.4.3. ECOG Performance Status

ECOG performance status will be summarized by cycle; ECOG performance status will be presented in data listing format.

9.3.4.4. Physical Examination

The analysis of physical examination will focus on patients who develop abnormalities post-baseline or whose evaluations worsen after baseline. Frequency tables will display the number and frequency of patients with any abnormalities. The results of abnormal physical examinations will also be listed.

9.3.5. Efficacy Analyses

- Response evaluation is based upon the Investigator's determination of response using RECIST v1.1 (Eisenhauer 2009). A response is defined as instance of a patient exhibiting a confirmed complete response (CR) or partial response (PR).

- Objective response rate (ORR) is defined as the number of patients exhibiting response divided by the number of patients qualified for tumor response analysis.
- Progression-free survival (PFS) is defined as the time from the first study drug dose to the first date of objectively determined disease progression or death from any cause. For patients who are still alive at the time of analysis and without evidence of tumor progression, PFS will be censored at the date of the most recent objective progression-free observation. For patients who receive subsequent anticancer therapy before objective disease progression or death, PFS will be censored at the date of the last objective progression-free observation before the date of subsequent therapy.
- Duration of response (DOR) is defined as the time from the date when the measurement criteria are met for CR or PR (whichever status is recorded first) until the date of first observation of objective disease progression. Duration of response will be censored at the date of the last objective progression-free disease assessment for patients who respond to treatment and die without progressive disease (excluding death from study disease). For responding patients not known to have died at the time of the data analysis and who do not have progressive disease, duration of response will be censored at the last progression-free assessment date. The disease control rate (DCR; CR + PR + stable disease) will be similarly analyzed.

  For responding patients who receive subsequent anticancer therapy (after discontinuation from all study treatment) before disease progression, duration of response will be censored at the date of last progression-free assessment before the initiation of post-discontinuation anticancer therapy.
- Duration of CR (DOCR) is defined as the time from the date when the measurement criteria are met for CR until the date of first observation of objective disease progression.
- Overall survival (OS) is defined as the time from the first study drug dose to the date of death from any cause. For patients who are still alive at the time of the analysis, OS time will be censored on the date of the patient's last contact.

9.3.6. Pharmacokinetic Analysis

9.3.7. Electrocardiogram Analysis

The proportions of patients with treatment-emergent clinically significant ECG abnormalities will be tabulated, and changes in ECG findings will be presented in data listing format. If warranted, categorical analyses of QTc interval data will be provided for the number and percentage of patients meeting or exceeding the following threshold values:

- Absolute QTc interval prolongation: QTc interval >450 ms, >480 ms, and >500 ms
- Change from Baseline in QTc interval: QTc interval increases >30 ms and >60 ms

9.3.8. Pharmacodynamic Analysis

PD analyses will be described in a separate Statistical Analysis Plan.

9.4. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Ethical, Legal, and Administrative Considerations

10.1.1. Informed Consent

Written informed consent in compliance with 21 Code of Federal Regulations (CFR) § 50 and/or International Council for Harmonisation (ICH) will be obtained from each patient before undergoing any protocol-specific tests or procedures that are not part of routine care.

The Sponsor will provide an ICF template to the Investigator for use in developing a study center-specific ICF. Prior to submission of the study center-specific ICF to the IRB/EC, the study center-specific ICF must be reviewed and approved by the Sponsor. Any changes requested by the IRB/EC must also be approved by the Sponsor. The final IRB/EC-approved ICF must be provided to the Sponsor. Revisions to the ICF required during the study must be approved by the Sponsor, and a copy of the revised ICF provided to the Sponsor.

Before recruitment and enrollment, each prospective patient (or legal guardian) will be given a full explanation of the study and be allowed to read the ICF. After the Investigator or designee is assured that the patient/legal guardian understands the commitments of participating in the study, the patient/legal guardian will be asked to sign and date the ICF.

A copy of the fully signed and dated ICF will be given to the patient. The original will be maintained in the patient's medical record at the study center.

10.1.2. Study Discontinuation and Closure

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and the Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of SL-901.

10.1.3. Confidentiality and Privacy

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from the Sponsor.

Patient confidentiality will be strictly maintained to the extent possible under the law. Patient names must not be disclosed. Patients will be identified on the eCRFs and other documents submitted to the Sponsor or its designated representative, by their initials and/or birth date and/or assigned patient number. Documents that identify the patient (e.g., the signed ICF) should not be submitted to and/or or its designated representative, and must be maintained in confidence by the Investigator.

10.1.4. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored by the Sponsor or designee. After the study is completed, the de-identified, archived data will be transmitted to and stored by the Sponsor, for use by other researchers including those outside of the study.

With the patient's approval and as approved by local IRB/EC, de-identified biological samples will be stored with the same goal as the sharing of data.

During the study, an individual patient can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological sample storage may not be possible after the study is completed.

10.1.5. Key Roles and Study Management

Study Sponsor:	Stemline Therapeutics, Inc. 750 Lexington Avenue 4th floor New York, NY 10022 Telephone: 1-646-502-2310 [redacted]
SAE Reporting:	STML-901-0119_PV@TigermedGrp.com

10.1.6. Clinical Monitoring

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

- Monitoring for this study will be performed by the Sponsor or designee.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.7. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written standard operating procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated in compliance with the protocol, GCP, and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.1.8. Data Handling and Record Keeping

The Investigator and designees agree to maintain accurate eCRFs and source documentation as part of case histories. Source documents are the originals of any documents used by the Investigator or Sub-Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the study.

The Sponsor will develop the Electronic Data Capture (EDC) environment to the study center. eCRFs must completed only by persons designated by the Investigator. All data entered into the eCRF must also be available in the source documents. The Investigator will allow the Sponsor designated representatives and regulatory bodies to have direct access to the source documents to verify the data reported in the eCRFs.

The CRA will review the eCRF data against source documents according to the CMP. Investigators are responsible for ensuring the accuracy and quality of the eCRF data.

A record of patient screen failures will be maintained for patients who do not qualify for enrollment. Minimal data entry is required for screen failed patients.

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study

10.1.9. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or other study requirements documented in any study-specific operational document. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions may need to be developed by the site and implemented promptly.

It is the responsibility of the Investigator to use continuous vigilance to promptly identify and report protocol deviations. All deviations must be addressed in study source

documents and reported to the Sponsor. Protocol deviations must be sent to the reviewing IRB/EC per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements.

10.1.10. Publication and Data Sharing Policy

All information regarding SL-901 supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor.

The Investigator agrees to use the Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of the Sponsor.

It is understood that there is an obligation to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used towards the development of SL-901 and may be disclosed by the Sponsor to regulatory authorities, other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee any publication or presentation of the study results, which will reflect the experience of all participating study centers. All publications and presentations must be approved in advance by the Sponsor in its sole discretion. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

10.1.11. Financial Disclosure Reporting Obligations

Investigators and Sub-Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its regulatory obligation. Investigators and Sub-Investigators must commit to promptly updating the information if any relevant changes occur during the study and for a period of one year after the completion of the study.

11. REFERENCES

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