STATISTICAL ANALYSIS PLAN

- Region 2 -

Study Title:	Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Topotecan Chemotherapy
Sponsor	G1 Therapeutics 79 T.W. Alexander Drive 4501 Research Commons, Suite 100 Research Triangle Park, NC 27709
Name of Test Drug:	G1T28
Protocol Number:	G1T28-03
Phase:	Phase 1b/2a
Analysis Plan Version	Version 1.0
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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
aRR	Adjusted Rate Ratio
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under Curve
β-HCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BOR	Best Overall Response
BPM	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CDK	Cyclin Dependent Kinase
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DSN	Duration of Severe Neutropenia
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of Infusion
ESA	Erythropoietin Stimulating Agent
FACT	Functional Assessment of Cancer Therapy
FACT-AN	Functional Assessment of Cancer Therapy –Anemia
FACT-L	Functional Assessment of Cancer Therapy –Lung
G1T28	Trilaciclib
GCSF	Granulocyte Colony-Stimulating Factor

Abbreviation	Term
HGB	Hemoglobin
HR	Hazard Ratio
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal Range
MAHE	Major Adverse Hematologic Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
Nadir	The Lowest Point
NCI	National Cancer Institute
NE	Not Evaluable
NLR	Neutrophil-Lymphocyte Ratio
NTL	Non-Target Lesion
OC	Observed Case
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PLR	Platelet-Lymphocyte Ratio
PP	Per Protocol
PR	Partial Response
PRO	Patient-Reported Outcome
PT	Preferred Term
QOL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SMC	Safety Monitoring Committee
SVN	Severe Neutropenia
SOC	System Organ Class
TEAE	Treatment-Emergent AE
TL	Target Lesion
TLFs	Tables, Listings, and Figures

Abbreviation	Term
TPR	Time Point Response
ULN	Upper Limit of Normal Range
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the analyses to be performed for Study G1T28-03, Phase 1b/2a Study of the Safety, Efficacy, and Pharmacokinetics of trilaciclib in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Topotecan Chemotherapy. The SAP is based on the G1T28-03 Protocol Version 6, dated 27 June 2018.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

The myelosuppression efficacy endpoints and statistical analysis methods described in this SAP are reflective of scientific advice obtained in both the US and EU for evaluation of trilaciclib for the reduction of chemotherapy-induced myelosuppression.

Although G1T28-03 does not explicitly state that the trial has been designed to evaluate the effects of trilaciclib on chemotherapy-induced myelosuppression, the endpoints of AEs and laboratory values used to evaluate safety and tolerability are the same endpoints used to evaluate effects on chemotherapy-induced myelosuppression. The data collected for this trial was appropriate for the analysis of these myelosuppression endpoints, and the defined endpoints in this SAP are consistent with the overall strategy/rationale for Study G1T28-03.

2. STUDY DETAILS

2.1. Study Objectives

The primary, secondary, and exploratory objectives of this study are presented in Table 1.

Table 1 G1T28-03: Study Objectives

	Part 1 (Phase 1b)	Parts 2A and 2B (Phase 2a)
Primary Objectives		
Assess the DLTs and define the Phase 2 dose of trilaciclib administered with topotecan	X	
Assess the safety and tolerability of trilaciclib administered with topotecan	X	X
Secondary Objectives		
Assess the PK profile of trilaciclib	X	X[a]
Assess the PK profile of topotecan when administered with trilaciclib	X	X[a]
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of trilaciclib administered with topotecan	X	X
Assess the incidence of febrile neutropenia	X	X
Assess the incidence of infections	X	X
Assess the utilization of RBC and platelet transfusions	X	X
Assess the utilization of hematopoietic growth factors	X	X
Assess the utilization of systemic antibiotics	X	X
Assess the incidence of chemotherapy dose reductions and dose interruptions overall	X	X
Assess the incidence of Grade 2 or greater nephrotoxicity	X	X
Assess tumor response based on RECIST, Version 1.1	X	X
Assess PFS and overall survival	X	X
Exploratory Objectives		
Assess the incidence of mucositis	X	X
Assess the incidence of alopecia	X	X
Assess the incidence of fatigue	X	X
Assess patient-reported QOL	X	X

Assess immunologic markers	X	X

DLT = dose-limiting toxicity; PFS = progression-free survival; PK = pharmacokinetic; QOL = quality of life; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

a Limited population PK sampling in Parts 2A and 2B

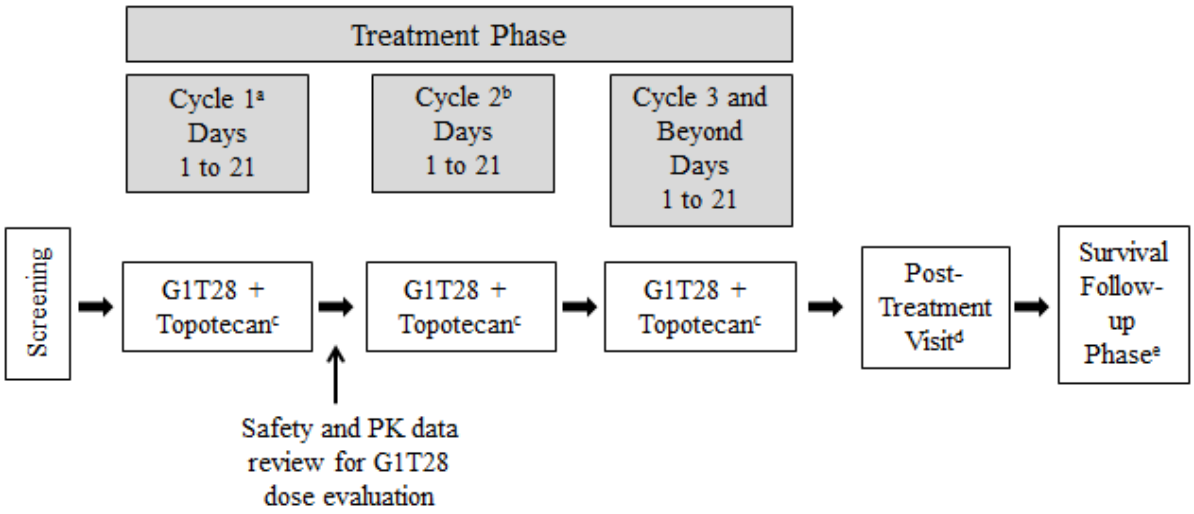
2.2. Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2a study of the safety, efficacy, and PK of trilaciclib in combination with topotecan for patients with previously treated extensive-stage SCLC. The study consists of 2 parts: a limited open-label, dose-finding portion (Part 1), and a randomized, double-blind, placebo-controlled portion (Parts 2A and 2B). All parts include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post Treatment Visit.

Part 1

The goal of Part 1 is to assess the safety, including dose-limiting toxicities (DLTs), and pharmacokinetics (PK) of trilaciclib administered at an initial dose of 200 mg/m^2 once daily in combination with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 1). DLTs are defined in Protocol section 6.1.1.1.

Figure 1 Study Schema: Part 1



a Safety and PK data from Cycle 1 will be considered in making dose escalation/de-escalation decisions (if required) and enrolling additional cohorts

b trilaciclib + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. The tumor should be assessed after every even cycle using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Assessments should be performed within 7 days of starting the subsequent cycle.

c trilaciclib will be administered prior to the administration of topotecan on Days 1 to 5 of 21-day cycles

d Patients will return to the study center for a Post-Treatment Visit at 30 days +3 days after the last dose of study drug (topotecan or trilaciclib/placebo).

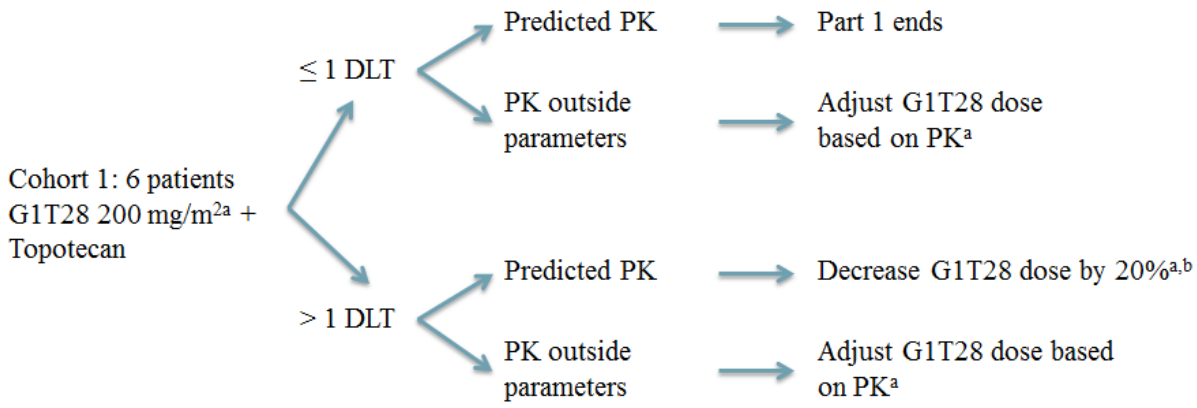
e The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B of the study have died.

Trilaciclib Dose Evaluation

Six patients will initially be enrolled in Part 1 and will receive an initial dose of trilaciclib 200 mg/m^2 in combination with standard topotecan therapy. Safety and PK parameters from this initial cohort of 6 patients during Cycle 1 will be considered in making dose escalation/de-escalation decisions (if required). If a patient is withdrawn prior to completing all assessments in Cycle 1 for reasons other than toxicity in any cohort in Part 1, the patient will be replaced. Trilaciclib dose evaluation criteria are listed below and are presented as a decision tree in Figure 2.

- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of Part 1 and the trilaciclib PK parameters are as predicted (Protocol Section 6.1.1.2), Part 1 will end, and all subsequent patients will be enrolled into Parts 2A and 2B, utilizing a dose of trilaciclib of 200 mg/m^2 in combination with topotecan.
- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of Part 1, and the trilaciclib PK parameters suggest that the trilaciclib dose needs to be escalated or de-escalated (see Protocol Section 6.1.1.2), a second cohort of 6 patients will be enrolled at the higher or lower predicted trilaciclib dose in combination with topotecan. For assessment of data from the second cohort enrolled in Part 1, please see the decision tree in Figure 2.
- If there is > 1 DLT in the first cohort of 6 patients during Cycle 1 of Part 1 and the trilaciclib PK parameters suggest that the trilaciclib dose needs to be escalated or de-escalated (see Protocol Section 6.1.1.2), a second cohort of 6 patients will be enrolled at the modified trilaciclib dose in combination with topotecan. For assessment of data from the second cohort enrolled in Part 1, please see the decision tree in Figure 2.
- If there is > 1 DLT in the first cohort of 6 patients enrolled in Part 1 and the trilaciclib PK parameters from these 6 patients are as predicted (Protocol Section 6.1.1.2), the dose of trilaciclib should be decreased to 160 mg/m^2 and an additional 6 patients should be enrolled at the modified trilaciclib dose in combination with topotecan. For assessment of data from the second cohort enrolled in Part 1, please see the decision tree in Figure 2.
- If there is > 1 DLT following a trilaciclib dose of 160 mg/m^2 in combination with topotecan and the PK parameters from these 6 patients are as predicted (Protocol Section 6.1.1.2), an additional cohort of 6 patients will be enrolled at a further decreased trilaciclib dose of 130 mg/m^2 in combination with topotecan. For assessment of data from the third cohort enrolled in Part 1, please see the decision tree in Figure 2.
- If there is > 1 DLT following the second dose reduction of trilaciclib and the PK parameters from these 6 patients are as predicted (Protocol Section 6.1.1.2), no further dose modifications will be made and the study will be terminated.
- At any time, if ≥ 2 DLTs are observed in any given cohort, further enrollment into that cohort will be stopped pending safety monitoring committee (SMC) review and recommendations for either continued enrollment or permanent closure of the cohort

Figure 2 Trilaciclib Dose Evaluation



a Assess the adjusted trilaciclib dose in the next cohort of 6 patients based on DLTs and PK per the decision tree

b Maximum of 2 trilaciclib dose reductions are allowed (first dose reduction to 160 mg/m^2 and second dose reduction to 130 mg/m^2)

All dose-escalation/de-escalation decisions will be based on Cycle 1 safety and available PK data and will be reviewed by a SMC composed of the sponsor, medical monitor, and the principal investigator(s) to determine the next dose level. If the trilaciclib and/or topotecan dose level for a subsequent cohort is adjusted by the SMC, the SMC may also recommend that all patients currently receiving trilaciclib in combination with topotecan should have their trilaciclib and/or topotecan dose adjusted accordingly, starting with their next scheduled cycle. Additional cohorts for Part 1 will be considered based on review of the safety and PK data by the safety monitoring committee. The doses of trilaciclib and topotecan for Arm 1 of Parts 2A and 2B will be obtained by utilizing all available safety and PK data from patients enrolled in Part 1. There will be no intrapatient dose modifications of trilaciclib in Parts 2A and 2B of the study.

Each patient will be evaluated for toxicity during each cycle. The toxicity of IV trilaciclib administered with topotecan will be assessed by the investigators using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Topotecan Dose Evaluation

Since trilaciclib has been shown to inhibit renal transporters for which topotecan is a substrate, there is a potential for increasing topotecan exposure when administered after trilaciclib. However, the relative contribution of these transporters in topotecan clearance has not been established. Therefore, in Part 1 of the present Study G1T28-03, PK of trilaciclib and topotecan will be assessed on Days 1 and 4 of the first cycle.

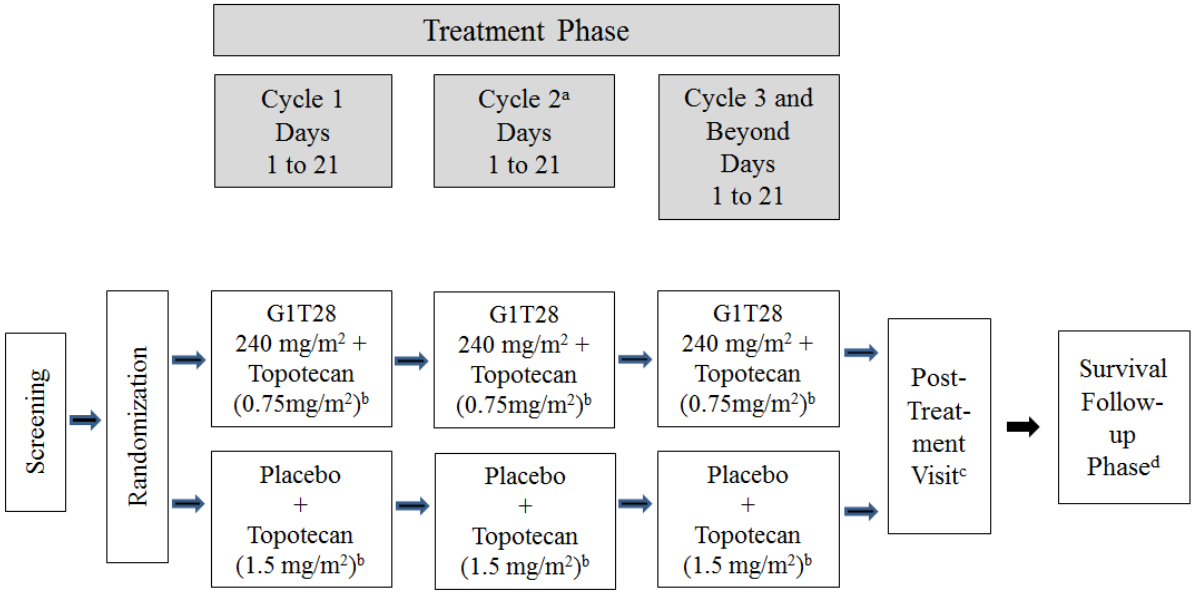
Since myelosuppression is the major toxicity of topotecan and trilaciclib is being developed to reduce myelosuppression following cytotoxic chemotherapy, complete blood count (CBC) monitoring will be followed closely in this study. If topotecan exposure is significantly altered resulting in potential safety concerns, the SMC will evaluate the data and modify the dose of topotecan as appropriate. In particular, the SMC will closely evaluate the safety data if the mean topotecan CL in the first 6 patients is ≤ 0.14 L/min/m^2.

Part 2A

In Part 2A, eligible patients will be randomized (2:1) to receive trilaciclib or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 3). In Arm 1, patients will receive the trilaciclib (240 mg/m^2) + topotecan (0.75 mg/m^2) doses originally determined in Part 1 of the study, and in Arm 2, patients will receive placebo + topotecan 1.5 mg/m^2.

Randomization will be stratified on the basis of Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and sensitivity to first-line treatment (sensitive: complete response (CR), partial response (PR), or stable disease (SD) after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: progressive disease (PD) as best response to first-line therapy or progression-free interval < 90 days after completion of first line therapy). There will be no intrapatient dose modifications of trilaciclib in Parts 2A of the study.

Figure 3 Study Schema: Part 2A



a Trilaciclib or placebo + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. The tumor should be assessed after every even cycle using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Assessments should be performed within 7 days of starting the subsequent cycle.

b Trilaciclib or placebo will be administered prior to the administration of topotecan on Days 1 to 5 of 21-day cycles

c Patients will return to the study center for a Post-Treatment Visit at 30 days +3 days after the last dose of study drug (topotecan or trilaciclib/placebo).

d The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B of the study have died.

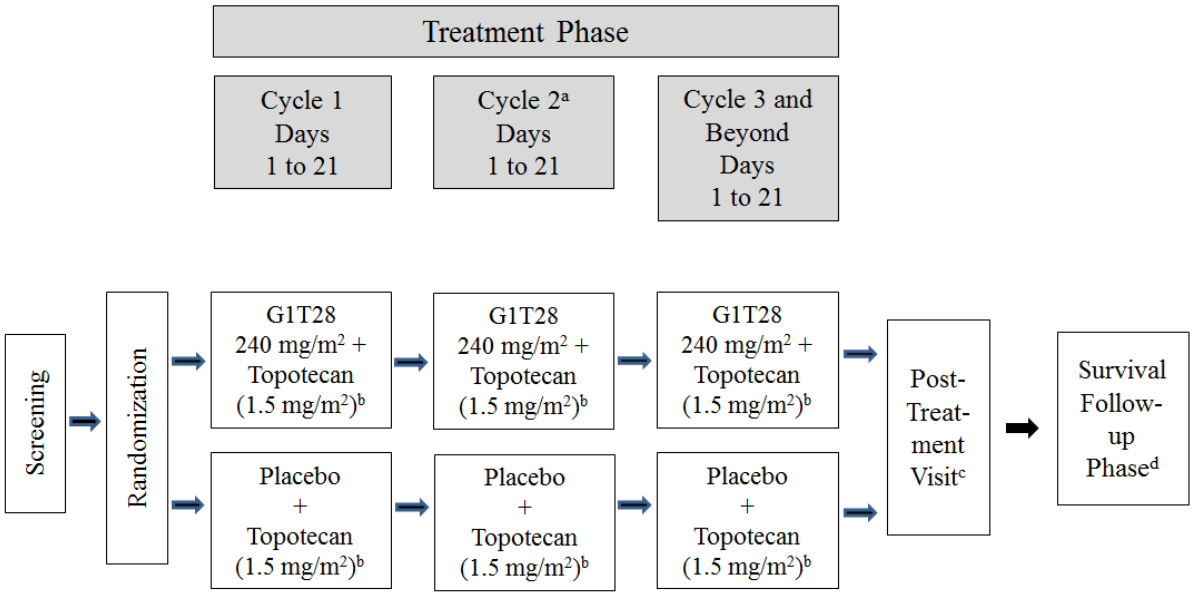
An independent data monitoring committee (DMC) will monitor accumulating safety and disposition data approximately every 4 months during the Treatment Phase of Part 2A of the study, depending upon the enrollment rate. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

Part 2B

Unblinded topotecan PK data in Part 2A suggested differences in the topotecan exposures in Arm 1 compared to Arm 2, with the differences being attributed to use of less accurate historical controls for topotecan. In order to accurately assess the impact of trilaciclib on the safety and efficacy of topotecan, it is critical that topotecan exposures are similar in the trilaciclib and placebo arms. Therefore, an additional arm of trilaciclib 240 mg/m2 + topotecan 1.5 mg/m2 will be investigated in Arm 1 of Part 2B in this study. In Part 2B, eligible patients will be randomized (2:1) to receive trilaciclib or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 4). In Arm 1, patients will receive trilaciclib (240 mg/mg^2) + topotecan (1.5 mg/m^2) and in Arm 2, patients will receive placebo + topotecan (1.5 mg/m^2).

As described above in Part 2A, randomization for Part 2B will also be stratified on the basis of ECOG performance status (0 or 1 versus 2) and sensitivity to first-line treatment (sensitive: CR/PR/SD after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: PD as best response to first-line therapy or progression-free interval < 90 days after completion of first-line therapy). There will be no intrapatient dose modifications of trilaciclib in Part 2B of the study.

Figure 4 Study Schema: Part 2B



a Trilaciclib or placebo + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. The tumor should be assessed after every even cycle using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Assessments should be performed within 7 days of starting the subsequent cycle.

b Trilaciclib or placebo will be administered prior to the administration of topotecan on Days 1 to 5 of 21-day cycles

c Patients will return to the study center for a Post-Treatment Visit at 30 days +3 days after the last dose of study drug (topotecan or trilaciclib/placebo).

d The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B of the study have died.

An independent DMC will monitor accumulating safety and patient disposition data in Part 2B, with the first meeting occurring after approximately 10 patients have been enrolled, and then

approximately every 4 months during the Treatment Phase, depending upon the enrollment rate. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

Criteria for Subsequent Cycles and Study Duration

In both parts of the study, study drug (topotecan or trilaciclib/placebo) administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons as described below.

In order to start Cycle 2 and subsequent cycles as scheduled, patients should meet all of the following criteria:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Nonhematologic drug-related toxicities (except alopecia) must be ≤ Grade 1 or have returned to baseline

A delay of up to 2 weeks is permitted to allow recovery from any toxicity in order to meet the continuation criteria for organ function. If patients meet the criteria for starting the subsequent cycle as described above, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). If the subsequent cycle is delayed, the patient should still complete the clinical laboratory assessments and the FACT-L and FACT-An questionnaires on the scheduled Day 1, as well as on the actual first dosing day of the next cycle. A patient will be discontinued from the study if recovery from any toxicity, in order to meet the continuation criteria for organ function, and any delay for administrative reasons requires a total delay of > 2 weeks.

After discontinuation of study drug (topotecan or trilaciclib/placebo), patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the completion of the patient-reported outcome (PRO) scales, CBC assessment on Day 22, the Post-Treatment Visit, and the Survival Follow-up Phase of the study.

The G1T28-03 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study. The total study duration is at least 33 months.

Part 1 is expected to be approximately 17 months, assuming 12 months of accrual, 2 weeks for screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.

Part 2A will begin after the Phase 2 doses of trilaciclib and topotecan (for Arm 1 of Part 2A) are identified from Part 1, which is expected to occur approximately 17 months after Part 1 begins (based on 12 months of accrual, 2 weeks of screening, 3 months of treatment, and time for the analysis of safety and PK data to identify the Phase 2 dose). Part 2A is expected to be approximately 16 months, assuming 11 months of accrual, 2 weeks of screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.

Part 2B will begin after enrollment in Part 2A is complete (ie, when approximately 45 patients are enrolled) and is expected to be approximately 14 months, assuming 9 months of accrual, 2 weeks of screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.

The Survival Follow-up Phase of the study will continue until at least 50% of the patients in Parts 2A and 2B have died. The study scheduled assessments are presented below:

Table 2 Schedule of Assessments

	Screening	Enroll	Cycle 1 and Odd Cycles[a] (21 days)								Cycle 2 and Even Cycles[a] (21 days)								Last Cycle	Post-Treatment Visit[b]	Survival Follow-up[c]
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**4**	**5**	**10**	**12**	**15**	**1**	**2**	**3**	**4**	**5**	**10**	**12**	**15**	**22**	**30 +3**	
Informed Consent[d]	X																				
Demographics	X																				
Medical History[e]	X																				
Eligibility Eval.	X	X																			
Performance Status	X		X								X									X	
Physical Exam	X		X								X									X	
Height, Weight & Vital Signs[f]	X		X								X									X	
Clinical Chemistry	X		X[g]							X	X[g]							X		X	
Hematology	X		X[h]				X	X	X	X[s]	X[h]				X	X	X	X[s]	X	X	
Urinalysis	X		X[g]								X[g]									X	
Immunologic markers[i]			X							X	X							X	X	X	
ECG[j]	X		X[j]			X[j]														X	
Pregnancy test[k]	X		X								X										
Randomization[r]		X																			
Tumor Assessment[l]	X[l2]																	X		X[l1, l2]	X[l1]
Tumor Testing[m]		X																			
PK[n]			X			X															
Trilaciclib or placebo[o]			X	X	X	X	X				X	X	X	X	X						

	Screening	Enroll	Cycle 1 and Odd Cycles[a] (21 days)								Cycle 2 and Even Cycles[a] (21 days)								Last Cycle	Post-Treatment Visit[b]	Survival Follow-up[c]
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**4**	**5**	**10**	**12**	**15**	**1**	**2**	**3**	**4**	**5**	**10**	**12**	**15**	**22**	**30 +3**	
Topotecan			X	X	X	X	X				X	X	X	X	X						
FACT-L and FACT-An[p]			X					X			X					X				X	
AEs[q]	X	X																			
Prior and Con. Medications	X	X																			
Survival Follow-up[c]																					X

AE = adverse event; ECG = electrocardiogram; FACT-AN = Functional Assessment of Cancer Therapy – Anemia quality of life instrument; FACT-L = Functional Assessment of Cancer Therapy – Lung quality of life instrument; PRO = patient reported outcome; Eval. = evaluation; PK = pharmacokinetic

a Trilaciclib + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. The tumor should be assessed after every even cycle. Assessments should be performed within 7 days of starting the subsequent cycle.

b Patients will return to the study center for a Post-Treatment Visit at 30 days (+ 3 days) after the last dose of study drug (topotecan or trilaciclib/placebo).

c Monthly phone calls will be made to each patient that is in the long-term Survival Follow-up Phase. Any anticancer therapies used will be collected. Patients will be followed for survival until at least 50% of the patients in Parts 2A and 2B have died. In addition, for patients who have not had disease progression at the time of study drug (topotecan or trilaciclib/placebo) discontinuation, tumor assessments, including all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

d Informed consent may be obtained up to 28 days prior to the first study treatment administration.

e Including medical, surgical, radiation history, smoking history, documentation of tumor diagnosis, baseline signs and symptoms within 4 weeks prior to the first dose of study drug (topotecan or trilaciclib/placebo), weight loss in the 6 months prior to the first dose of study drug (topotecan or trilaciclib/placebo) (≤ 5% or > 5%), and medications taken within 14 days prior to the first dose of study drug (topotecan or trilaciclib/placebo).

f Height will only be measured at the screening visit. Body surface area calculation (based on actual body weight taken prior to study drug (topotecan or trilaciclib/placebo) administration) will be completed on Day 1 of each cycle and vital signs obtained immediately before and after trilaciclib and topotecan infusions on Day 1. Vitals only need to be taken once between the infusions.

g Clinical chemistry will be obtained (albumin, alkaline phosphatase [ALP], total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase [LDH], sodium, and blood urea nitrogen [BUN]); see Protocol Section 11.3.2. Clinical chemistry and urine analysis may be obtained up to 72 hours prior to the first dose of each cycle of trilaciclib + topotecan.

h Hematology will be obtained (hemoglobin, hematocrit, white blood cells (WBCs) with differential, and platelet counts); see Protocol Section 11.3.2. Hematology may be obtained up to 24 hours prior to first dose of each cycle of trilaciclib + topotecan.

i For patients who choose to participate in the optional immunophenotyping portion of the study, peripheral blood will be collected at predose on Day 1 and Day 15 of each cycle; Day 22 of the last cycle; and at the Post-Treatment Visit. Immunophenotyping samples may be obtained up to 24 hours prior to first dose of each cycle of trilaciclib + topotecan.

j Patients participating in Part 1 of the study will have ECGs completed at the following time points on Days 1 and 4 of Cycle 1: predose, 0.5 hour (end of infusion [EOI] of trilaciclib), 1 hour (± 10 minutes), and 6.5 hours (± 15 minutes) after start of trilaciclib infusion. Patients participating in Parts 2A and 2B of the study will have ECGs completed at the following time points on Day 4 of Cycle 1: predose, 0.5 hour (EOI of trilaciclib), 1 hour (± 10 minutes), and between 3.5 to 6.5 hours (± 15 minutes) after start of trilaciclib infusion.

k For female patients of childbearing potential, serum ß-hCG at screening; serum or urine ß-hCG, obtained up to 72 hours prior to each dose of trilaciclib + topotecan chemotherapy in each cycle

l For tumor assessment, all sites of disease (including brain metastases, if present at screening) should be assessed radiologically by CT or MRI at screening and after every even cycle, until the occurrence of disease progression. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. Assessments may be performed within 7 days of starting the subsequent cycle. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If PET is used, it should also be accompanied by spiral CT or MRI.

l1: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug (topotecan or trilaciclib/placebo) discontinuation (may be performed within 4 weeks of treatment discontinuation). For those patients in the survival follow-up who have not progressed at the time of study drug (topotecan or trilaciclib/placebo) discontinuation, tumor assessments, including all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

l2: Brain scans with contrast (by CT or MRI) to be obtained with tumor assessment at screening (within 28 days of dosing). For those without brain metastases at screening, an additional scan should be performed at the Post-Treatment Visit for patients who have not progressed at the time of study drug (topotecan or trilaciclib/placebo) discontinuation (may be performed within 4 weeks of treatment discontinuation). For those with brain metastases, brain scans should be done with each tumor assessment.

m Send archived tumor samples to a central pathology laboratory to confirm the diagnosis of SCLC. Available tissue after confirming the diagnosis of SCLC will be banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the CDK4/6 pathway. If central pathology review does not confirm SCLC diagnosis, the patient may be withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor. This should be done as soon as possible after a patient has enrolled in the study.

n Patients enrolled in Part 1 will have trilaciclib and topotecan PK samples collected on Days 1 and 4 (as applicable) of Cycle 1 at the time points specified in Protocol Section 11.3.2. In addition, limited PK samples will be collected on Cycle 1 Day 4 in Parts 2A and 2B of the study for trilaciclib population PK analysis. Blood samples will be collected in Parts 2A and 2B of the study at the time points specified in Protocol Section 11.3.2.

o Trilaciclib or placebo will be administered as an IV infusion in 250 mL of D5W or sodium chloride solution 0.9% over 30 (± 5) minutes prior to topotecan chemotherapy on Days 1 to 5 of every cycle (see Protocol Section 11.3.2). If there is any study drug (topotecan or trilaciclib/placebo) remaining in the trilaciclib infusion bag at the end of the 30 (± 5) minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. The interval between doses of trilaciclib on successive days should not be greater than 28 hours. The interval between the dose of trilaciclib and the dose of topotecan on a given day should not be greater than 4 hours. Trilaciclib will only be administered with topotecan. If administration of topotecan is discontinued, trilaciclib should also be discontinued. Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If the second, third, fourth, or fifth dose of trilaciclib in any given cycle is not administered for any reason, do not administer the dose of topotecan on that day (see Protocol Section 11.3.2). After discontinuation of study drug (topotecan or trilaciclib/placebo), patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported PRO (scales), CBC assessment on Day 22, the Post-Treatment Visit, and the Survival Follow-up Phase of the study.

p Patient-reported outcomes should be completed at Days 1 and 10 of each cycle and at the Post-Treatment Visit. If a cycle is delayed, the patient should still complete the PRO on the scheduled Day 1 of the next cycle, as well as the actual first dosing day of the next cycle of trilaciclib + topotecan. Patient-reported outcomes may be obtained up to 24 hours prior to the first dose of each cycle of trilaciclib + topotecan.

q Adverse events will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug (topotecan or trilaciclib/placebo), and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

r For patients enrolled in Parts 2A and 2B, randomization is to be done within 3 days prior to the first dose of trilaciclib or placebo + topotecan, following confirmation that the patient is eligible for the study.

s Patients with an ANC $< 0.5 \times 10^9$/L on Day 15 shall be followed (eg, every 24 to72 hours) for recovery (to ensure that duration of ANC $< 0.5 \times 10^9$/L does not exceed 7 days).

2.3. Number of Patients

Overall, approximately 130 patients will be enrolled in the study. In Part 1, approximately 40 patients will be enrolled, assuming 9-10 cohorts. Part 1 is open label and no randomization or blinding will be required. In Part 2A, approximately 45 patients will be enrolled and randomly assigned (2:1) to Arm 1 (trilaciclib (240 mg/m^2) + topotecan (0.75 mg/m^2)) or Arm 2 (placebo+ topotecan (1.5 mg/m^2)). In Part 2B, approximately 45 patients will be enrolled and randomly assigned (2:1) to Arm 1 (trilaciclib (240 mg/mg^2) + topotecan (1.5 mg/m^2)) or Arm 2 (placebo + topotecan (1.5 mg/m^2)).

The sample size is not determined from a statistical perspective, but rather is based on clinical feasibility. Subjects who receive placebo in Part 2A and Part 2B will be combined into a single placebo group for the analysis. Thus, approximately 90 patients will be enrolled into Part 2 of the study (30 per treatment group).

With the changes to the protocol detailed in this SAP, the sample size calculation is now based on demonstrating the superiority of trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) vs. placebo+ topotecan with respect to at least one of the primary endpoints.

With the changes, the overall type I error rate is now 0.10 (1-sided) and the type II error rate used to compute sample size is 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using the most conservative Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.10/2=.05 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 2 days between the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group and the placebo+ topotecan group requires, 56 evaluable patients (28 per treatment arm in the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group and the placebo + topotecan group). This implies that 90 patients need to be randomized for all 3 groups assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for placebo + topotecan group, testing for an absolute reduction of 37% to 8% with the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group would require a sample size of at least 56 patients (29 per treatment arm in the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group and the placebo + topotecan group). Assuming a 95% evaluability rate, at least 90 patients for Part 2 of the study need to be randomized for all 3 groups to complete the study. Therefore, the final adjusted sample size is 90 for Part 2 of the study to account for the evaluation of 2 primary endpoints. All calculations were carried out using the POWER procedure in SAS® version 9.4.

The study will be conducted at up to 60 centers in North America and Europe.

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

Data analyses will be based on the four analysis sets defined below. Analysis sets, including exclusions based on key deviations, will be reviewed and approved by G1 Therapeutics prior to study unblinding.

3.1.1. Intent-to-Treat Analysis Set

The intent-to-treat analysis set (ITT) includes all randomized patients in Part 2 and all enrolled patients who received at least one dose of study drugs in Part 1. Analyses using the ITT will be conducted on the basis of the assigned treatment. The ITT is the primary analysis set for all efficacy analysis.

3.1.2. Modified ITT Analysis Set

The modified ITT (mITT) analysis set is a subset of the ITT analysis set and will only include the ITT patients who received at least 1 dose of study drug (topotecan or trilaciclib/placebo). Supportive sensitivity analyses will be conducted on the mITT analysis set for primary and key secondary efficacy endpoints to evaluate the robustness of the results. Analyses using the mITT will be conducted on the basis of the assigned treatment.

3.1.3. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least 1 dose of study drug (topotecan or trilaciclib/placebo). Analyses using the safety analysis set will be conducted on the basis of the actual treatment received. All safety analyses will be assessed using the safety population.

3.1.4. Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set. The criteria for inclusion in the PP analysis set will be based on study drug (topotecan or trilaciclib/placebo) administration and key protocol deviations; the list of patients to be included in this analysis set will be finalized and documented prior to unblinding patients in Parts 2 of the study.

It will include only those patients who have no exclusionary protocol deviations (as described in Section 3.2) and who received the treatment to which they were randomized or assigned. For any patients who received the wrong treatment during any part of the study, their data will be excluded from the PP analysis set. The PP analysis set may be used to analyze selected endpoints to test the robustness of results.

3.1.5. Response Evaluable Analysis Set

The Response Evaluable Analysis Set will include all patients who are in the mITT, have measurable disease (target lesions) at the baseline tumor assessment, and either (i) have at least 1 post-baseline tumor assessment, (ii) have clinical progression as noted by the investigator before their first post-baseline tumor scan, or (iii) have died due to disease progression before their first post-baseline tumor scan. The response evaluable analysis set will be used for sensitivity analyses of tumor response.

3.2. Protocol Deviations

Certain protocol deviations are designated as key in that they may affect the ability to assess the safety and efficacy of study drug (topotecan or trilaciclib/placebo). All key protocol deviations will be reviewed in a data review meeting to discuss the potential impact on the statistical analysis and classify each key deviation as exclusionary or non-exclusionary. This will be documented in a note to file prior to database lock and Part 2 unblinding.

Patients with key deviations determined to impact the analysis will be excluded from the PP analysis set. All patients who meet the definition of the ITT/mITT analysis sets will be included in the ITT/mITT analysis sets regardless of these deviations.

If a patient is randomized or assigned to a treatment group, but fails to receive treatment, the reason for not receiving treatment will be noted in the CSR. Any such patients who are not treated will be excluded from the mITT, safety, response evaluable, and PP analysis sets but will be included in the ITT (for Part 2) and in the patient listings for the CSR.

If the wrong treatment is administered to a patient, and the reason for the incorrect treatment is documented, this will be noted in the CSR and the patient's data included in the Safety Analysis Set based on the actual treatment received.

4. PROSPECTIVELY DEFINED ANALYSES

As outlined in the protocol, trilaciclib is an IV Cyclin Dependent Kinase (CDK) 4/6 inhibitor being evaluated for its ability to decrease chemotherapy-induced myelosuppression when administered in combination with cytotoxic chemotherapy. Unlike granulocyte-colony stimulating factor (GCSF), which stimulates production of neutrophils, and transfusions, which only replace red blood cell (RBC) or platelets, trilaciclib is hypothesized to facilitate myelopreservation of all hematopoietic lineages including neutrophils, RBC, platelets, lymphocytes, etc.

To capture these two aspects of trilaciclib benefit, the following analyses are prospectively proposed in Table 3 and their associated endpoint derivation and analysis methods will be detailed in Sections 5.1.1 and 6.2.7.1 with the multiplicity adjustments described in Section 5.1.1.

Table 3 Prospectively Defined Analyses

Occurrence (proportion of patients) of severe (Grade 4) neutropenia
Duration of severe (Grade 4) neutropenia in Cycle 1
Occurrence (proportion of patients) of RBC transfusions on/after 5 weeks
Occurrence (proportion of patients) of GCSF administration
Occurrence (proportion of patients) of Platelet transfusion
Cumulative incidence of major adverse hematologic events (MAHE) which is defined to include components as the following: • All-cause hospitalizations • All-cause dose reductions • Febrile neutropenia • RBC transfusion on/after 5 weeks • Prolonged severe (Grade 4) neutropenia (duration > 5 days) • Platelet transfusion
All-cause hospitalizations in the MAHE composite
All-cause dose reductions in the MAHE composite
Febrile neutropenia in the MAHE composite
RBC transfusions on/after 5 weeks in the MAHE composite
Prolonged severe (Grade 4) neutropenia in the MAHE composite
Platelet transfusions in the MAHE composite

RBC = Red Blood Cell; GCSF = granulocyte-colony stimulating factor;

5. PRIMARY AND SECONDARY ENDPOINTS

The following general definitions will be applied to all endpoint derivations unless otherwise specified.

Term	Definition
Severe Neutropenia (SVN)	ANC lab value that meets the common terminology criteria for adverse events (CTCAE) criteria for ≥ Grade 4 toxicity
Cycle baseline	The last non-missing value within the window starting from 3 days prior to the date/time of study drug (topotecan or trilaciclib/placebo) administration on Day 1 of Cycle 1 and 1 day prior to Day 1 of each subsequent cycle (i.e. Cycle 2, Cycle 3, etc.); must be prior to the time of study drug (topotecan or trilaciclib/placebo) administration
Cycle nadir	The lowest value for a given hematologic parameter that occurs between start of cycle and end of cycle and is less than the cycle baseline.
Duration of cycle	Total number of days from start of cycle to end of cycle, that is, date of end of a cycle - date of start of cycle + 1.
End of cycle*	Day 1 of the subsequent cycle. For example, the end of cycle for Cycle 1 is Day 1 of Cycle 2. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 38 after the first dose of the cycle.
Start of cycle	Day 1 of each cycle starts with the administration of study drug(s) (topotecan or trilaciclib/placebo)
Start of study	Date of enrollment in Part 1 or Date of randomization in Part 2
Study baseline	The last non-missing value prior to, or on the date of administration of study drug(s) (topotecan or trilaciclib/placebo); must be prior to the time of study drug administration
Change from baseline	Calculated as the post-baseline value minus the baseline value. If the baseline value is missing for a particular endpoint, change from baseline will be missing.
Treatment period	Total number of days from start of cycle for Cycle 1 and end of cycle for the last cycle

* For various hematologic parameter analyses, the last assessment prior to end of cycle will be utilized in the analyses. Situations where this applies will be indicated as such.

5.1. Efficacy endpoints

5.1.1. Primary Endpoints

5.1.1.1. Occurrence of Severe (Grade 4) Neutropenia

For the treatment period, the total number of SVN events is the number of cycles where at least one ANC value is $< 0.5 \times 10^9$/L. For example, if Cycle 2 has two ANC values that are both $< 0.5 \times 10^9$/L, this only counts as one event. If a patient did not have any SVN events, the value of 0 will be assigned to that patient. The number of cycles without SVN is calculated as the total

number of cycles received – total number of cycles with SVN. Unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

Therefore, any occurrence of an SVN during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes, if total number of cycles with SVN ≥ 1 is observed, No for other scenarios.

5.1.1.2. Duration of Severe (Grade 4) Neutropenia (DSN)

There will be three different strategies for assessing DSN in each cycle. All strategies will be applied to derive the DSN, with strategy 1 considered as the primary, and strategy 2 and strategy 3 being supportive sensitivity analyses. The DSN in Cycle 1 is considered the primary endpoint. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation of each strategy.

5.1.1.2.1. Strategy 1: Without Imputation of Missing ANC Values

Within each cycle, the DSN (days) is defined as the number of days from the date of first ANC value of $<0.5\times10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5\times10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5\times10^9$/L and (2) no other ANC values $<0.5\times10^9$/L occur between this day and end of cycle. DSN is set to 0 in patients who did not experience SVN in a cycle. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation. The following rules will be applied in the calculation:

- For a cycle where the SVN event does not resolve by end of the cycle, DSN will be assigned as above except the end date will be the end of cycle.
- For a cycle where the patient dies, during the SVN event, DSN will be assigned as above except the end date will be the date of death.
- For a cycle where the patient withdraws consent or is lost to follow-up during the SVN event, DSN will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of study.

5.1.1.2.2. Strategy 2: Without Imputation, Censoring Unresolved SVN

Within each cycle, DSN (days) is defined as the number of days from the date of first ANC value of $<0.5 \times 10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5 \times 10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5 \times 10^9$/L and (2) no other ANC values $<0.5 \times 10^9$/L occur between this day and end of cycle. The following censoring rules will be applied in the calculation:

- For a cycle where the SVN event does not resolve by end of the cycle, DSN will be assigned as above except the end date will be the earlier of end of cycle or date of last contact.
- For a cycle where the patient dies, withdraws consent, or is lost to follow-up during the SVN event, DSN will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of study.

For the treatment period, the overall DSN (days) is the median value among the DSN (days) from all cycles. The following data handling conventions will apply:

- For those patients where all event duration values are derived from cycles with censored data, the median value for that patient will be the median censored value. It will be a considered a censored value;
- For those patients where a subset of event duration values are derived from cycles with censored data, the median value for that patient will be estimated using the Kaplan-Meier method. It will be considered as an observed value (i.e. no censored value);
- For those patients where the median event duration cannot be derived (e.g. ≤ 2 values), the longest event duration amongst all the cycles will be used regardless of censoring, but the corresponding censoring flag will be carried over for analysis.

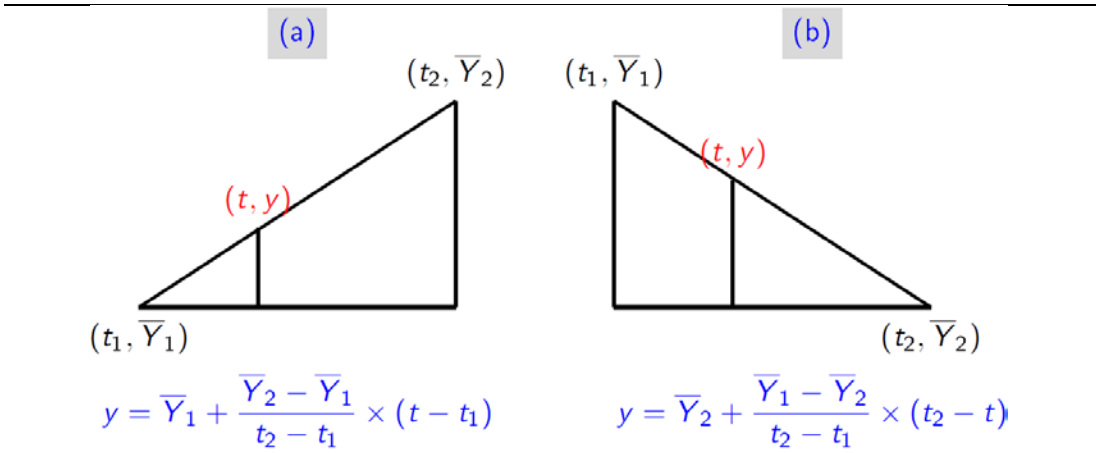
5.1.1.2.3. Strategy 3: With Imputation of Missing ANC Values

DSN (days) in a cycle is defined as the number of consecutive days with SVN, for patients who experienced several episodes of SVN, the number of days for each episode will be summed up. DSN is set to 0 in patients who did not experience SVN in a cycle.

To impute the missing daily ANC value, the following algorithms will be applied in the calculation,

(1) Missing ANC values for Days 1-5 in each cycle will be imputed using linear interpolation, any recorded measurement will not be replaced. The missing values for Day 1 and Day 5 may be potentially imputed with this algorithm.

Figure 5 Graphical Demonstration of Linear Interpolation



Note: The slopes are calculated for each treatment group, where $\bar{Y}_1$ and $\bar{Y}_2$ are the mean of ANC values at relevant timepoint. For a time interval, e.g. interval of Day 1 and Day 5 (inclusive), $\bar{Y}_1$ is the average of the earliest point in the interval and t_1 is the average of the earliest day in the interval. Similarly, $\bar{Y}_2$ is the average of the latest point in the interval and t_2 is the average of the latest day in the interval.

- If there are at least two assessments within the interval of Day 1 and Day 5 (inclusive), calculate the slope between the first available ANC value and last available ANC value:

  - If the sign of slope agrees with the sign of slopes calculated from its treatment group, the interpolation will be conducted to appropriate schemes as demonstrated in Fig.1 (a) and Fig. 1(b);
  - If the sign of slope does not agree with the sign of slopes calculated from its treatment group, the interpolation will be done within the patient by using the calculated slope from the observed values.
- If there is only one assessment within the interval of Day 1 and Day 5 (inclusive),
  - If the ANC value is $< 0.5\times10^9$/L, then the subsequent missing days will be set to this value;
  - If ANC value is $\geq 0.5\times10^9$/L, SVN cannot be determined, and the data remains missing.
- If there is no assessment within the interval of Day 1 and Day 5 (inclusive), SVN cannot be determined, and the data remains missing.

(2) A similar algorithm as in (1) will be performed to impute missing ANC values for Days 6-10 in each cycle using linear interpolation. Day 5 will be used as the earliest date in the calculations only if it is recorded; it will be interpolated in this interval. Any other recorded measurements will not be replaced.

(3) Rules of imputation of missing values at Day 11 of a cycle:

- The ANC before and after the missing day was $\geq 0.5\times10^9$/L: the day is ignored as a potential day of severe neutropenia.
- If at either neighboring days the ANCs were $< 0.5\times10^9$/L, and both are non-missing, then the missing day is set to severe neutropenia.
- If any of the neighboring days were also missing, severe neutropenia cannot be determined, and the data remains missing.

(4) A similar algorithm as in (1) will be performed to impute missing ANC values for Days 12-15 in each cycle using linear interpolation. Any recorded measurements will not be replaced.

(5) A similar algorithm as in (1) will be performed to impute missing ANC values between Days 16 and end of cycle in each cycle using linear interpolation. Day 15 will be used as the earliest date in the calculations only if it is recorded; it will be interpolated in this interval. Any other recorded measurements will not be replaced.

(6) For a cycle where the SVN event does not resolve by end of the cycle, the all values between the last assessment and the end of cycle are set to SVN.

(7) For a cycle where the patient dies, during the SVN event, the end date of the SVN is the date of death.

5.1.2. Key Secondary Endpoints

5.1.2.1. Occurrence of RBC Transfusions

Each RBC transfusion with a unique start date on/after 5 weeks on study during the treatment period will be defined as a separate event and included in the efficacy analyses. A sensitivity analysis including all events occurring during the treatment period will also be performed.

Occurrence of an RBC transfusion during the treatment period is defined as a binary variable (Yes or No); Yes if total number of RBC transfusions ≥ 1 is observed, No for other scenarios.

5.1.2.2. Occurrence of GCSF Administrations

Administration of GCSF is collected with the concomitant medications which are coded using World Health Organization Drug Dictionary (WHO-DD Version Sep2017). The criterion to select proper records is as follows: If the chemical subgroup from WHO-DD Version Sep2017 (i.e. TEXT4 for CODE4) takes value "COLONY STIMULATING FACTOR", the medication is classified as GCSF.

A cycle where GCSF is administered concurrently will be identified by comparing the start and stop dates of each administration of GCSF to the start of cycle and end of cycle. If any of the dates of administration of GCSF overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having GCSF administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number GCSF administrations is the number of cycles in which there is at least one GCSF dose administered. If a patient did not have any GCSF use, the value of 0 will be assigned to that patient. The number of cycles where GCSF was NOT given is calculated as total number of treatment cycles received – total number of cycles where GCSF was administered.

Therefore, any occurrence of a GCSF administration during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with GCSF administration ≥ 1 is observed, No for other scenarios.

5.1.2.3. Occurrence of Platelet Transfusions

Each platelet transfusion with a unique start date during the treatment period will be defined as separate event.

Occurrence of a platelet transfusion during the treatment period is defined as a binary variable (Yes or No); Yes if total number of platelet transfusions ≥ 1 is observed, No for other scenarios.

5.1.2.4. Occurrence of All-Cause Dose Reductions

Dose (mg/m^2) reductions are not permitted for trilaciclib. Dose reductions for topotecan are collected on the dosing page.

No more than 2 dose reductions for toxicity in total are allowed for any patient. All dose reductions will be counted as a separate event. For more details see Section 5.2.1.4.

5.1.2.5. Overall Survival

Although OS is a key secondary endpoint, OS will be analyzed with a descriptive intention and will not be factored into multiplicity adjustment as described in Section 6.2.7.1.4. That is, no formal statistical testing will be planned. The analysis of OS will be primarily aimed at showing lack of harm from trilaciclib.

Overall survival is calculated as the time (months) from date of first dose of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2 to the date of death due to any cause. Patients who do not die during the study will be

censored at the date last known to be alive. Patients lacking data beyond the day of first dose of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2 will have their survival time censored at day of first dose of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2. OS will not be censored if a patient receives other anti-tumor treatments after the study drugs (topotecan or trilaciclib/placebo).

5.1.3. Supportive Secondary Efficacy Endpoints

5.1.3.1. Total Number of Major Adverse Hematologic Event (MAHE)

As a composite measure of trilaciclib effect, MAHE is based on a combination of individual components specified in Table 4, which also include details about the derivation or data source for each component. For each component of composite MAHE, the number of events is derived as the number of episodes with a unique start date during the treatment period between the date of the start of Cycle 1 and the end of the last cycle (i.e. last cycle of placebo or trilaciclib plus topotecan). A patient without an episode will be assigned a value of 0 for the number of events for this component. Then, the total number of MAHE during the treatment period is obtained as the summation over all components of composite MAHE during the treatment period.

Table 4 Component of MAHE and the Suggested Data Source/Derivation Algorithm

Seq #	Component of MAHE	Details
1	All-cause hospitalizations	Each hospitalization is captured in the AE data of the electronic database. Each recorded Preferred Term (PT) with a unique start date will be counted as an event, e.g. if a patient is hospitalized and several preferred terms are attributed to that hospitalization with the same start date, then the event is only counted once. The event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
2	All-cause dose reductions	Detailed in Section 5.1.2.4
3	Febrile neutropenia	Detailed in Section 5.1.3.9
4	Prolonged severe (Grade 4) neutropenia (duration > 5 days)	Detailed in Section 5.1.1.2.1. Each cycle with a duration greater than 5 days will be counted as an event with the date of the first grade 4 lab value defined as the start date for the time-to-first event analysis.
5	RBC transfusion on/after 5 weeks	Detailed in Section 5.1.2.1
6	Platelet transfusion	Detailed in Section 5.1.2.3

A patient without an episode of MAHE will be assigned a value of 0 for the overall total number of MAHE. Additionally, a sensitivity analysis will be done for dose reductions and RBC transfusions on/after 5 weeks, that excludes patients who do not start a second cycle of treatment.

Time to first occurrence of a MAHE will be used as a sensitivity analysis in support of the total number of MAHE. It is defined as the first time to observe an event among all the components, starting from the date of the start of Cycle 1. Therefore, for a patient with a MAHE, time (months) to first occurrence of a MAHE will be the minimum among the 6 potentially derived durations (i.e. calculated as (date of first occurrence of a MAHE component event – date of Start of Cycle 1 + 1)/30). A patient without any MAHE will be censored at the end of the last cycle (i.e. last cycle of placebo or trilaciclib), death, end of study, or date of last contact, whichever is earlier.

5.1.3.1.1. All-Cause Hospitalizations

See Section 5.1.3.1

5.1.3.1.2. Prolonged severe (Grade 4) neutropenia (duration > 5 days)

See Section 5.1.3.1.

5.1.3.2. Best Overall Response, Duration of Response, and Progression-Free Survival

For tumor assessment, all sites of disease will be assessed radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) at screening and every 2 months thereafter, until the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009) or by clinical criteria; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. At each tumor assessment visit, the overall visit response by RECIST will determined two ways: (1) derived programmatically using the information from target lesions (TL), non-target lesions (NTLs) and new lesions as entered into the eCRF, and (2) by the investigator and collected in the eCRF.

For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1 and the best overall response (BOR).

5.1.3.2.1. Target Lesions (TLs)

Measurable disease is defined as having at least one measurable lesion which is

- ≥10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥15 mm) with CT or MRI; or
- ≥10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); or
- ≥ 20 mm by chest X-ray.

Previously irradiated lesions (or lesions treated with loco-regional therapies) may be considered measurable if unequivocal growth of the lesion has been demonstrated. A patient can have a maximum of 5 measurable lesions representative of all involved organs (maximum of 2 lesions per organ, both the lymph node and skin will be considered as a single organ) recorded at baseline and these are referred to as target lesions. If more than one baseline scan is recorded, then measurements from the one that is closest to start of treatment will be used to define the baseline sum of TLs. Table 5 gives definition of TL visit responses.

Table 5 Definition of TL Visit Responses

Visit Reponses	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters (i.e. nadir) since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Rounding of TL data

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a target lesion response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

If any target lesion measurements are missing, then the target lesion visit response is Not Evaluable (NE). The overall visit response will also be NE, unless there is a progression of non-target lesions or new lesions, in which case the response will be PD.

TL too small to measure

If a target lesion becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured.

Lesions that split

If a TL splits, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 cm.

Change in method of assessment of target lesions

CT, MRI, chest x-ray and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination and chest x-ray only used in special cases. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

5.1.3.2.2. Non-Target Lesions (NTLs) and New Lesions

The non-target lesion response will be based on the Investigator's overall assessment of NTLs as Table 6:

Table 6 Definition of NTLs Visit Responses

Visit Reponses	Description
CR	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10mm short axis).
PD	Unequivocal progression of existing NTLs, which may be due to an important progression in one lesion only or in several lesions
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression
NE	Only relevant when one or some of the NTLs have not been assessed and in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment.

New lesions

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses. A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL responses.

5.1.3.2.3. Time Point Response (TPR)

Table 7 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give a TPR. The possible TPRs at a visit are CR, PR, SD, PD, and NE.

Table 7 Evaluation of Time Point Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/not all evaluated	No	PR
SD	Non-PD/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

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

At each visit, patients will be programmatically assigned a RECIST Version 1.1 TPR of CR, PR, SD, PD or NE depending on the status of their disease compared to baseline and previous assessments as discussed in the Sections 5.1.3.1.1 and 5.1.3.1.2.

For a scheduled tumor assessment, it is expected that there will be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the derived overall assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the *same* target lesions, the last assessment will be used.

5.1.3.2.4. Best Overall Response (BOR) and Duration of Response (DOR)

BOR will be determined using TPRs up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009) or by clinical criteria; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. BOR will not be derived for those patients who do not have measurable target lesions.

A patient's BOR will be determined based on Table 8. For data-driven scenarios which may not be covered by Table 8, the BOR will be reviewed and determined by the medical advisors and statisticians prior to unblinding the study.

For patients who progress and subsequently have a response, the best overall response is only derived from assessments up to and including the time of the progression (i.e., it will not include the response after the patient has progressed).

There are two ways of assigning BOR for a patient when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of patients in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized.

Table 8 Best Overall Response When Confirmation of CR and PR are Required [a]

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not available.

a. The minimum interval for confirmation of CR and PR is 4 weeks.

b. Best response will be SD if the first time point overall response is after 35 days on study. Otherwise, the best response will be PD.

c. Best response will be SD if the first time point overall response if after 35 days on study. Otherwise, the best response will be NE.

d. Best response will be SD provided the criteria for PD have not been met from the first to second assessment.

* A best overall response of SD can only be made after the subject is on study for a minimum of 35 days (counted from Cycle 1 Day 1). If the subject is on study for less than 35 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

^Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR.

Objective response rate (ORR) will be calculated using two methods:

Method #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes (0/1) variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with objective response being "Yes".

Method #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes (0/1) variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with objective response being "Yes".

Duration of Response (DOR) is the time between first response by RECIST Version 1.1 of CR or PR and the first date that progressive disease is documented by RECIST Version 1.1 or death. Patients who do not experience PD or death will be censored at the last tumor assessment date. Only those patients with confirmed responses will be included in this analysis. Censoring will follow the rules outlined below for progression-free survival (PFS) in Section 5.1.3.1.5.

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of confirmed CR, confirmed PR, or SD.

ORR, $ORR_{UNCONFIRMED}$, DOR and CBR will be calculated using the derived responses and investigator responses.

5.1.3.2.5. Progression-free Survival

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented.

Hence, PFS is defined as the time (months) from date of first dose date of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2 until date of documented disease progression or death due to any cause, whichever comes first. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

PFS will be calculated using derived responses and progression by RECIST Version 1.1 will be considered.

Death, regardless of cause, is always considered as a PD event. The detailed censoring rules for the analysis are summarized in Table 9.

Table 9 Assignment of Progression or Censoring Based on Radiological Assessment

Situation	Date of Progression or Censoring	Outcome
No Baseline assessment	Date of first dose of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2	Censored
No progression - treatment not started	Date of first dose of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2	Censored

Situation	Date of Progression or Censoring	Outcome
No progression	Date of last adequate radiological disease assessment	Censored
Treatment discontinuation for reasons other than disease progression	Date of last progression assessment with no documented progression	Censored
New anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment no later than the initiation of new anticancer treatment	Censored
Disease progression per RECIST Version 1.1	Date of the first reported progression	Progressed
Death without a PD	Date of death	Progressed
Determination of clinical progression per the investigator	Date of the investigator assigned PD	Progressed [a]

[a] For the primary derivation of PFS, the clinical progression will not be included (i.e. it will only be based on radiologic progression), but it will be incorporated as a separate derivation of PFS, and its analysis will be considered to be supportive.

Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer therapy occur on the same day, will assume that the progression was documented first, *e.g.* outcome is progression and the date is the date of the assessment of progression.

5.1.3.3. Occurrence of Grade 3 and 4 Hematologic toxicities

Hematologic toxicity events are defined as any cycle where any hematologic lab value occurs that meets the CTCAE toxicity grade criteria for ≥ Grade 3 and the value is treatment emergent. For details on which parameters are included and the definition of treatment emergent see Section 5.2.4.

For the treatment period, the total number of hematologic toxicity events is the number of cycles in which there is at least one hematologic toxicity event. If a patient did not have any hematologic toxicity events, the value of 0 will be assigned to that patient. The number of cycles without hematologic toxicity events is calculated as total number of treatment cycles received – total number of cycles with a hematologic toxicity event.

Therefore, any occurrence of a hematologic toxicity event during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with a hematologic toxicity event ≥ 1 is observed, No for other scenarios.

5.1.3.4. ANC Nadir by Cycle

See table in Section 5 for the definition of cycle nadir.

5.1.3.5. ANC, Platelet Count, Absolute Lymphocyte Counts (ALC), and Hemoglobin Change over Time

For the hematologic parameters consisting of ANC, hemoglobin, platelet count, and ALC, the observed lab values in each windowed visit as detailed in Section 6.1.3 will be appropriately identified for further analysis.

5.1.3.6. Occurrence of Erythropoietin Stimulating Agent (ESA) Administrations

Administration of ESAs is collected with the concomitant medications which are coded using WHO-DD Version Sep2017. The criterion to select proper records is as follows: If the chemical subgroup from WHO-DD Version Sep2017 (i.e. TEXT4 for CODE4) takes value "OTHER ANTIANEMIC PREPARATIONS", the medication is classified as ESAs.

Those cycles where ESAs are administered concurrently will be identified by comparing the start and stop dates of each ESA to the start of cycle and end of cycle. If any of the dates of administration of an ESA overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having an ESA administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number ESA administrations is the total number of cycles in which there is at least one ESA dose administered. If a patient did not have any ESA use, the value of 0 will be assigned to that patient. The number of cycles where ESAs were NOT given is calculated as total number of treatment cycles received – total number of cycles where ESAs were administered.

Therefore, any occurrence of an ESA administration during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with an ESA administration ≥ 1 is observed, No for other scenarios.

5.1.3.7. Occurrence of IV Antibiotic Uses

IV antibiotic administration is collected with concomitant medications which are coded using WHO-DD Version Sep2017. The criteria for identifying an IV antibiotic administration event is

- If the Therapeutic subgroup from WHO-DD Version Sep2017 (i.e. TEXT2 for CODE2) takes value "ANTIBACTERIALS FOR SYSTEMIC USE", and
- The route of medication is "intravenous" or the route is "other" with the detailed specification as "IVPB".

Each IV antibiotic with a unique start date during the treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

Occurrence of an IV antibiotics administration during the treatment period is defined as a binary variable (Yes or No); Yes if total number of IV antibiotics administrations ≥ 1 is observed, No for other scenarios.

5.1.3.8. Occurrence of Infection Serious Adverse Events (SAEs)

Each infection SAE is captured in the electronic database. The event terms are coded using the MedDRA Version 20.1. The criterion for identifying the proper infection SAE records is as

follows: if the system organ class (SOC) from MedDRA takes value "INFECTIONS AND INFESTATIONS" and the AE is a serious event.

Each infection SAE with a unique start date during the treatment period will be defined as separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.1.

Any occurrence of an infection SAE during the treatment period is defined as a binary variable (Yes or No); Yes if total number of infection SAEs ≥ 1 is observed, No for other scenarios.

5.1.3.9. Occurrence of Pulmonary Infection SAEs

Each pulmonary infection SAE is captured in the electronic database. The event terms are coded using the MedDRA Version 20.1. The criterion for identifying the pulmonary infection SAEs records is as follows: if the system organ class (SOC) from MedDRA takes value "INFECTIONS AND INFESTATIONS", the PT takes a values from Table 10 and the AE is a serious event.

Table 10 PT List for Grouping Infection AEs and Pulmonary Infection AEs

Category	Preferred terms
Pulmonary Infection AEs	Bronchiolitis
	Bronchitis
	Infectious pleural effusion
	Influenza
	Lung infection
	Pneumonia
	Pneumonia bacterial
	Pneumonia pneumococcal
	Respiratory tract infection
	Upper respiratory tract infection
	Viral upper respiratory tract infection

Each pulmonary infection SAE with a unique start date during the treatment period will be defined as separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.1.

Any occurrence of a pulmonary infection SAE during the treatment period is defined as a binary variable (Yes or No); Yes if total number of pulmonary infection SAEs ≥ 1 is observed, No for other scenarios.

5.1.3.10. Occurrence of Febrile Neutropenia

Each febrile neutropenia event is captured in AE data of electronic database, and "FEBRILE NEUTROPENIA" is a preferred term which can be used to identify the proper AE records. The event terms are coded using the MedDRA Version 20.1.

Each febrile neutropenia event with a unique start date during the treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.1.

Any occurrence of a febrile neutropenia event during the treatment period is defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios.

5.1.3.11. Occurrence of Grade 4 and Grade 3/4 Thrombocytopenia

Thrombocytopenia events of Grade 4 or Grade 3/4 are defined as any cycle where any platelet lab value occurs that meets the CTCAE toxicity grade criteria for ≥ Grade 4 (3) and the value is treatment emergent. For the definition of treatment emergent see Section 5.2.4.

For the treatment period, the total number of thrombocytopenia events is the number of cycles in which there is at least one thrombocytopenia event. If a patient did not have any thrombocytopenia events, the value of 0 will be assigned to that patient. The number of cycles without thrombocytopenia events is calculated as total number of treatment cycles received – total number of cycles with a thrombocytopenia event.

Therefore, any occurrence of a thrombocytopenia event during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with a thrombocytopenia event ≥ 1 is observed, No for other scenarios.

5.1.3.12. Myelosuppression Endpoints with All data up to End of Cycle 4

The following myelosuppression endpoints will be derived for a period of interest utilizing all available data up to the end of Cycle 4. The period of interest starts from the date of randomization/first dose of study drug, whichever is earlier. The end dates of the period depend on the status of each patient; for patients who receive ≤ 4 cycles of therapy, the period ends on the date of the first dose date of the last cycle + 38 days, and for patients who receive > 4 cycles, the period ends on Day 1 of Cycle 5. The derivation of each endpoint will follow the definition described in each relevant section.

- Occurrence of severe (Grade 4) neutropenia (Section 5.1.1.1);
- Occurrence of RBC transfusions on/after week 5 of study (Section 5.1.2.1);
- Occurrence of GCSF administrations (Section 5.1.2.2);
- Occurrence of platelet transfusions (Section 5.1.2.3);
- Total number of MAHE (Section 5.1.3.1);
- Number of all-cause hospitalizations (Section 5.1.3.1.1);
- Number of all-cause dose reductions (Section 5.1.2.4);
- Number of febrile neutropenias (Section 5.1.3.1);
- Number of cycles with prolonged severe (Grade 4) neutropenia (duration > 5 days) (Section 5.1.3.1.2);
- Number of RBC transfusions on/after 5 weeks (Section 5.1.3.1);
- Number of platelet transfusions (Section 5.1.3.1);
- Occurrence of Grade 3 and 4 hematologic toxicities (Section 5.1.3.3);
- Occurrence of RBC transfusions during the first 4 cycles (Section 5.1.2.1);
- Number of RBC transfusions during the first 4 cycles (Section 5.1.3.1);

5.1.4. Exploratory Efficacy Endpoints

5.1.4.1. FACT-L and FACT-An

The FACT-L and FACT-An analyses will be documented separately and are not covered in this SAP.

5.1.4.2. Grade 2 or Greater Nephrotoxicity

For any post-baseline creatinine assessment, an event of grade ≥ 2 nephrotoxicity is defined as the observed value >1.5 × baseline value, or > 1.5 × Upper Limit of Normal Range (ULN).

Within a cycle, for each nephrotoxicity event, the occurrence of a creatinine value meeting the criteria outlined above is described using a binary variable (Yes or No); Yes, if the designated event is observed, No for other scenarios. For the treatment period, the total number of nephrotoxicity events where the creatinine value meets the criteria is the number of cycles where at least one lab value meets the criteria. For example, if Cycle 2 has two values that both meet criteria, this only counts as one event. If a patient does not have any lab values meeting the criteria, the value of 0 will be assigned to that patient. Unscheduled data and the actual assessment date (rather than visit date) will be used for these analyses.

Any occurrence of a Grade ≥ 2 nephrotoxicity during the treatment period is defined as a binary variable (Yes or No); Yes if total number of Grade ≥ 2 nephrotoxicity events ≥ 1 is observed, No for other scenarios.

5.1.4.3. Occurrence of Alopecia and Mucositis

Alopecia will be identified by the preferred term of "alopecia", and mucositis will be identified by the high level term 'stomatitis and ulceration', or the preferred terms 'mucosal inflammation', 'mucosal ulceration', or 'oesophagitis' used in MedDRA Version 20.1 coding for AE data, and these terms will be used to identify the occurrence of events during the treatment period. Separate analyses will be done for each term.

Any occurrence of an alopecia (or mucositis) event during the treatment period is defined as a binary variable (Yes or No); Yes if total number of alopecia (or mucositis) events ≥ 1 is observed, No for other scenarios. Total number of events per subject will also be summarized. Data handling conventions for missing start/stop dates of AEs are in Section 5.2.1.

5.1.4.4. Neutrophil-lymphocyte Ratio (NLR) and Platelet-lymphocyte Ratio (PLR)

NLR will be derived using the ANC and ALC, and PLR will be calculated using platelet count and ALC. Both NLR and PLR may have prognostic value in patients with various solid tumors. That is, the lower the value, the better the clinical prognosis. If data permit, NLR and PLR will be correlated with various anti-tumor efficacy analyses [e.g. ORR, PFS, and etc.].

5.2. Safety Endpoints

5.2.1. Chemotherapy Exposure Endpoints

5.2.1.1. Duration of Exposure

Duration of exposure (days) = First dose date of study drug (topotecan or trilaciclib/placebo) from the last cycle – first dose date of study drug (topotecan or trilaciclib/placebo) + 21.

5.2.1.2. Number of Cycles Received

Patients are considered to have started a cycle if they have received at least one dose of any study drug (topotecan or trilaciclib/placebo). In addition to the numeric summary for the number of cycles, the number of cycles will be categorized as 1, 2, 3, 4, 5 to 10, and > 10.

5.2.1.3. Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 11.

Table 11 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Trilaciclib §	Topotecan ^
Dosing schedule per protocol	200 mg/m^2 IV on Days 1 to 5 of a 21-day cycle	1.5 mg/m^2 IV on Days 1 to 5 of a 21-day cycle
Dose by cycle	Total dose administered (mg) /most recent BSA (m^2) [(mg/m^2)].	Total dose administered (mg)/most recent BSA (m^2) [(mg/m^2)].
Cumulative dose	Sum of the doses administered to a patient in the duration of exposure [(mg/m^2)]	Sum of the doses administered to a patient in the duration of exposure [(mg/m^2)]
Dose intensity	Cumulative dose (mg/m^2) / (duration of exposure / 7) [(mg/m^2/week)]	Cumulative Dose (mg/m^2) / (duration of exposure / 7) [(mg/m^2/week)]
Relative dose intensity (%)	100 * [Dose intensity (mg/m^2/week) / (1000 /3 (mg/m^2/week)]	100 * [Dose intensity (mg/m^2/week) / (7.5 /3 (mg/m^2/week)]
Relative Dose (%)	100 * [Cumulative dose (mg/m^2) / (1000 × number of cycles (mg/m^2)]	100 * [Cumulative dose (mg/m^2) / (7.5 × number of cycles (mg/m^2)]

§ Three different doses (200mg/m^2, 240mg/m^2, and 280mg/m^2) of trilaciclib were evaluated in Part 1. 240mg/m^2 trilaciclib was the planned dose for all patients in Part 2. The calculation of relevant parameters will be adjusted accordingly based on the example presented in this table.
^ Four different doses (0.75mg/m^2, 1mg/m^2, 1.25mg/m^2, and 1.5mg/m^2) of topotecan were evaluated in Part 1. 0.75mg/m^2 and 1.5mg/m^2 were the planned dose for patients in Part 2. The calculation of relevant parameters for Part 1 will be adjusted accordingly based on the example presented in this table. Part 2 dosing amounts were not collected to preserve the blind and these parameters will not be calculated for it.
BSA = body surface area; IV = intravenous.

Total number of doses will be calculated and summarized by treatment.

5.2.1.4. Modifications of Study Therapy, Including Cycle (Dose) Delay, Missed Doses, Dose Interruptions, and Dose Reductions

- After Cycle 1, patients need to meet pre-specified laboratory parameter criteria before initiating Cycle 2 and each subsequent cycle of chemotherapy. Cycle (dose) delay and its associated reasons are collected at the beginning of each cycle in an eCRF page titled "Beginning Cycle Assessment". The reasons for delay will be summarized in the following categories: (1) Adverse event, (2) Logistical/Administrative Issues, (3) Hematologic Toxicity (which is a sum of those patients who fall into either category 3a or 3b), (3a) ANC < 1.5 x 10^9/L, (3b) Platelet Count < 100 x 10^9/L, (5) Nonhematologic Toxicity and (6) Other. Note that categories 3a and 3b are sub-bullets of category (3).
- Missed doses are identified on the dosing page of each study drug (topotecan or trilaciclib/placebo) based on the question "Was the dose missed?". The missed dose information will be obtained for each study drug (topotecan or trilaciclib/placebo). For a study drug (topotecan or trilaciclib/placebo), if the last record of response to question "Was the dose missed?" is Yes, it will not be considered as a missed dose but instead considered to be end of treatment if both criteria below are met:
    - No other study drugs (topotecan or trilaciclib/placebo) are given on the same day, and
    - No study drugs (topotecan or trilaciclib/placebo) are given subsequently.

  The reasons for missed doses will be summarized in the following categories: (1) Adverse Event, (2) Logistical/Administrative Issues, and (3) Other.
- Dose reductions are not permitted for trilaciclib. Dose reductions for topotecan are collected on the dosing page; the reasons for reduction will be summarized in the following categories: (1) Adverse Event, (2) Change recommendation by SMC, and (3) Other. No more than 2 dose reductions of topotecan for toxicity in total are allowed for any patient. Toxicity that requires dose reduction more than twice will lead to discontinuation of trilaciclib or placebo + topotecan; discontinuations will not be counted as a dose reduction. All dose reductions for toxicity are permanent, and no dose increases are allowed when dose reductions are made for toxicity.
- Dose interruptions for all drugs are also captured on the dosing page and will be summarized for each study drug (topotecan or trilaciclib/placebo).

5.2.2. Adverse Events

All AEs will be coded from verbatim text to PTs and grouped by SOC using the MedDRA Version 20.1. AEs will be collected from the time of signature of informed consent throughout the treatment period and up to 30 days after the last dose of study treatment. AEs are graded by investigator according to CTCAE, Version 4.03.

Any AE that started on or after the first dose of study drugs (topotecan or trilaciclib/placebo) and up to the last dose + 30 days will be included as a treatment emergent AE (TEAE). AEs with an unknown/not reported onset date will also be included.

Other AE variables include drug-related AEs, AEs leading to study drug (topotecan or trilaciclib/placebo) discontinuation or study withdrawal, AEs leading to death, and SAEs.

AEs with onset/end dates that are partially/completely missing will be imputed as follows:

(i) For onset date:

- If only the day part of the AE onset date is missing and occurs in the same month and year as the first dose date of study drug (topotecan or trilaciclib/placebo), the date of first dose of study drug (topotecan or trilaciclib/placebo) will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE;
- If the day and month parts of the AE onset date are missing and occur in the same year as the first dose of study drug (topotecan or trilaciclib/placebo), the date of the first dose of study drug (topotecan or trilaciclib/placebo) will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE;
- If the AE onset date is completely missing, the date of the first dose of study drug (topotecan or trilaciclib/placebo) will be used as the onset date of the AE.

(ii) For end date:

- If only the day part of the AE end date is missing, the last day of the month will be used to complete the end date of the AE;
- If the day and month parts of the AE end date are missing, December 31st will be used to complete the end date of the AE;
- If the AE end date is completely missing and the onset date of the AE occurs after the date of the first dose of study drug (topotecan or trilaciclib/placebo), the last date during the treatment period + 30 days will be used as the AE end date. If the AE end date is completely missing and the onset date of the AE occurs prior to the date of the first dose of study drug (topotecan or trilaciclib/placebo) the date of the first dose of study drug (topotecan or trilaciclib/placebo) will be used as the AE end date.

AEs related to hematologic toxicity will be pooled based on the preferred MedDRA Version 20.1. Table 12 outlines those terms that will be consolidated.

Table 12 Preferred Terms to Be Consolidated

Presented term in the table	Preferred Term
Neutropenia	Neutropenia
	Neutrophil count decreased
Febrile neutropenia	Febrile neutropenia
Anaemia	Anaemia
	Anaemia macrocytic
	Red blood cell count decreased
	Hemoglobin decreased
Thrombocytopenia	Thrombocytopenia

Presented term in the table	Preferred Term
	Platelet count decreased
Lymphopenia	Lymphopenia
	Lymphocyte count decreased
Leukopenia	Leukopenia
	White blood cell count decreased

AEs potentially related to infusion reactions will be pooled based on the PTs of MedDRA Version 20.1. The events described by the PTs listed below will be summarized and presented in order of decreasing frequency: Infusion site pain, Infusion site pruritus, Infusion site reaction, Infusion site burning, Infusion related reaction, Infusion site irritation, Infusion site redness, Allergic reaction, Catheter site itching, Catheter site erythema, Catheter site hematoma, and Catheter site pain..

5.2.3. Vital Signs

Vital signs include pulse rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height (only measured at screening), and body temperature. Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2, Body Surface Area (BSA) will be computed using DuBois-DuBois formula as $0.20247 \times [\text{height (m)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated. Vitals will be summarized by visit as collected and not windowed.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 13:

Table 13 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion value	Change from baseline
SBP	≥180 mmHg	Increase ≥40 mmHg
	≤ 90 mmHg	Decrease ≥40 mmHg
DBP	≥105 mmHg	Increase ≥20 mmHg
	≤ 50 mmHg	Decrease ≥20 mmHg
Pulse	≥ 120 bpm	Increase ≥40 bpm
	≤ 50 bpm	Decrease ≥40 bpm
Weight	n/a	Change ≥10%

bpm = beats per minute

5.2.4. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 14 will be measured.

Table 14 Laboratory Assessment

Lab Category	Lab tests
Hematology	Hemoglobin (HGB), hematocrit, white blood cell (WBC), platelet counts, ANC, ALC, Monocyte Absolute, Basophil Absolute, and Eosinophil Absolute.
Chemistry	albumin, Alkaline Phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), sodium, and Blood Urea Nitrogen (BUN).
Urinalysis	semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin microscopic examination, including RBC, WBC, and casts will be performed, if necessary

Change from baseline in laboratory test results to each assessment will be calculated; for hematology parameters, the change from cycle baseline will also be obtained. The urinalysis and hematocrit results will not be summarized; they will only be included in listings.

Clinical laboratory results will be graded according to CTCAE criteria, Version 4.03 which can be found in Table A-1 of Appendix. Any graded abnormality that occurs following the initiation of study drug (topotecan or trilaciclib/placebo) and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- ALT and/or AST >3x ULN, ALP < 2xULN, and Total Bilirubin> 2x ULN
- AST > 3,5,8,10, and 20x ULN, AST>5x ULN for more than 5 weeks
- ALT > 3,5,8,10, and 20x ULN, ALT > 5x ULN for more than 5 weeks
- Total Bilirubin >1.5 or >2x ULN

5.2.5. Electrocardiograms

Electrocardiogram (ECG) parameters include heart rate, PR interval, and QT, QTcB, QTcF and QRS intervals. Change from baseline to each post-baseline visit will be calculated and summarized by visit as collected and not windowed. Visits and timepoints only collected for PK subjects in Part 1 will be listed but not summarized.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 15. ECG results are interpreted as normal, abnormal but not clinically significant, or abnormal and clinically significant.

Table 15 Potentially Clinically Significant Criteria for ECG

ECG Parameter	Criterion value
Heart Rate	>120 bpm
	<50 bpm
PR Interval	≥ 210ms
QRS Interval	≥ 120ms
	≤ 50ms
QT Interval	≥ 500ms
	≤ 300ms
QTcB, QTcF Intervals	≥ 500ms
	≥ 480ms
	≥ 450ms
	≤ 300ms
	Change from baseline ≥ 30 ms
	Change from baseline ≥ 60 ms

5.2.6. Physical Examination

Physical examination is conducted during screening, on Day 1 of each cycle, and at the post-treatment visit. Abnormal findings in PE were to be reported as AEs. These data will not be summarized, i.e. they will only be available in listings.

6. ANALYSIS METHODS

6.1. General Principles of Analysis

6.1.1. General Methodology

In general, all efficacy, safety and PK variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Survival estimates will be analyzed with Kaplan-Meier method and summarized with median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CI), if applicable. Individual data will be presented in patient listings.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings. Upon completion, all SAS® programs will be validated by an independent programmer within the staff of the third-party vendor doing the primary analysis. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings.

All summary tables, listings, and figures (TLFs) will be presented by treatment groups as defined in Table 16.

Table 16 Treatment Display in TLFs

Study Part	Trilaciclib Dose	Topotecan Dose	Treatment Description in Data Display
Part 1	200 mg/m^2	1.5 mg/m^2	Cohort 1
Part 1	200 mg/m^2	1.25 mg/m^2	Cohort 2
Part 1	200 mg/m^2	0.75 mg/m^2	Cohort 3
Part 1	240 mg/m^2	0.75 mg/m^2	Cohort 4 & 6
Part 1	280 mg/m^2	0.75 mg/m^2	Cohort 5
Part 1	240 mg/m^2	1.0 mg/m^2	Cohort 7
Part 1	Any	Any	Total
Part 2	Placebo	1.5 mg/m^2	Placebo
Part 2	240 mg/m^2	0.75 mg/m^2	Trilaciclib 240 mg/m^2 and Topotecan 0.75 mg/m^2
Part 2	240 mg/m^2	1.5 mg/m^2	Trilaciclib 240 mg/m^2 and Topotecan 1.5 mg/m^2
Part 2	240 mg/m^2	Any	Total

All statistical tests will be presented at a two-sided .20 alpha level unless otherwise specified. The primary comparison will be conducted between placebo group (from Part 2A and 2B) and Trilaciclib 240 mg/m^2 + Topotecan 1.5 mg/m^2 group. Where appropriate, model-based point estimates, together with their 80% CIs will be presented along with the two-sided p-values for

the tests. P-value will be presented to 4 decimal places, if the p-value <0.0001, the value will be presented as "<0.0001".

For continuous data, the same number of decimal places as in the raw data will be presented when reporting mean, median, minimum and maximum; one more decimal place than in the raw data will be presented when reporting standard deviation and standard error (SE). The derived variables will be presented with 1 decimal place. Percentages will be reported with 1 decimal place; if the count is 0, no percentage will be presented. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but ≥ 99.5% will be presented as ">99%."

6.1.2. Handling of Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing — no missing imputation will be performed. Safety analyses will be conducted on the OC data only. However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. Please refer to Section 5.2.1 for the method of imputation of missing AE onset and stop date and Section 6.2.5 for the method of imputation of missing concomitant onset and stop dates.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Patients with missing data will be excluded only from analyses for which data are not available.

For the efficacy analyses, missing data will be excluded except for the sensitivity analyses noted in Section 6.2.7.1.4.

6.1.3. Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug (topotecan or trilaciclib/placebo) within each cycle – defined as Day 1 – to the dates that the scheduled visits occur. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 17. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patient listings.

For windowed visits during the treatment cycles, if more than 1 visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used. For the assigned follow-up visit, the last assessment in the window will be included in the summary.

For a patient who prematurely discontinues the study, the visit will be slotted accordingly. The window for post-treatment visit will be "the first dose date of the last cycle + 38 to last assessment date prior to the start of survival follow-up". Day 18 was collected in earlier versions of the protocol but will not be summarized as most cycles did not include.

Table 17 Visit Windowing

	Cycle x						Post-treatment [d]
Visit	**CxD1**	**CxD5**	**CxD10**	**CxD12**	**CxD15**	**EOCx**	
Scheduled Day [a]	1	5[e]	10	12	15[e]	22	
Clinical Chemistry [b]	Day -3 - 1				2 to EOC		From first dose date of last cycle to first dose date of last cycle + 38
Hematology [c]	Day -3 - 1	1 to 7	8 to 10	11 to 13	14 to 17	18 to EOC	

[a] The scheduled day is relative to the Day 1 of each cycle.
[b] Clinical chemistry may be obtained up to 72 hours prior to the first dose of each cycle.
[c] Hematology may be obtained up to 24 hours prior to dosing on Days 1, 3, 10, 12 and 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.
[d] 30 ± 3 days after the last dose of study drug (topotecan or trilaciclib/placebo)

6.1.4. Adjustment for Covariates

Patient randomization in Part 2 was stratified by ECOG performance status (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive: CR/PR/SD after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: PD as best response to first-line therapy or progression-free interval < 90 days after completion of first line therapy). The efficacy analyses will use the stratification factors as covariates in statistical models.

6.2. Analysis Methods

6.2.1. Patient Disposition

A summary table will be generated to provide the following by study part, as appropriate:

- Number of patients screened
- Number and percentage of screening failures
- Reason for screening failure
- Number of patients dosed
- Number of patients randomized (Part 2 only)
- Number of patients randomized and not dosed (Part 2 only)

A separate table will be presented to show the patients included in each analysis set and reason for exclusion from an analysis set.

Patient status at treatment and study completion will be listed and summarized. The listing will include whether patients discontinued from the treatment and the reasons for the discontinuation, along with the date of first and last dose and the date of completion or discontinuation from the treatment. The same information will be provided for patients who discontinued from the study. The following summaries will be added to the disposition table:

- End of treatment status
  - Reason for study drug (topotecan or trilaciclib/placebo) discontinuation
- Number of patients going into Survival follow-up
- Number and percentage of patients who discontinued the study
- Reason for study discontinuation
- Death and reason for death

6.2.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics, such as age at informed consent date, age groups (18-65, >65-75, >75), race, ethnicity, gender, screening vital signs (height, body weight, BMI, BSA), ECOG status (0 or 1, 2), sensitivity to first line treatment (sensitive, resistant, or unknown), and smoking history (never smoked, former smoker, and current smoker) will be summarized and listed.

6.2.3. Disease Characteristics

Disease characteristics including confirmation of diagnosis using neuroendocrine markers (Yes or No) and weight loss in the 6 months prior to randomization (Yes or No; if Yes, ≤5% or >5%),

will be summarized and listed. Family history of cancer and date of initial diagnosis of lung cancer will be listed only.

6.2.4. Medical History

Medical history will be coded to SOC and PT using MedDRA Version 20.1.

The number and percentage of enrolled patients (Part 1) or randomized patients (Part 2) with any past medical history within each SOC and PT will be provided. A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT). The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry.

Surgical history (Yes or No; and if Yes, related to lung cancer) will be summarized and listed. Concomitant surgeries will be listed.

6.2.5. Concomitant Medications

All medication verbatim terms collected will be coded to Anatomical Therapeutic Classification (ATC) and PT using the WHO-DD Version Sep2017.

Prior medications are defined as those taken by the patient prior to the administration of study drug (topotecan or trilaciclib/placebo). Concomitant medications are defined as those taken by the patient at any time between the date of study drug (topotecan or trilaciclib/placebo) administration and study completion/discontinuation. Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

Medications with onset/end dates that are partially/completely missing will be imputed as follows:

(i) For onset date:

- If only the day part of the medication onset date is missing and occurs in the same month and year as the first dose date of study drug (topotecan or trilaciclib/placebo), the date of first dose of study drug (topotecan or trilaciclib/placebo) will be used as the onset date of the medication. Otherwise, the first day of the month will be used to complete the onset date of the medication;
- If the day and month parts of medication onset date are missing and occur in the same year as the first dose of study drug (topotecan or trilaciclib/placebo), the date of the first dose of study drug (topotecan or trilaciclib/placebo) will be used as the onset date of the medication. Otherwise, January 1st will be used to complete the onset date of the medication;
- If the medication onset date is completely missing, the date of the first dose of study drug (topotecan or trilaciclib/placebo) will be used as the onset date of the medication.

(ii) For end date:

- If only the day part of the medication end date is missing, the last day of the month will be used to complete the end date of the medication;

- If the day and month parts of the medication end date are missing, December 31st will be used to complete the onset date of the medication;
  - If the medication end date is completely missing and the onset date of the medication occurs after the date of the first dose of study drug (topotecan or trilaciclib/placebo), the last date during the treatment period will be used as the medication end date. Otherwise, the date of the first dose of study drug (topotecan or trilaciclib/placebo) will be used as the medication end date.

Concomitant medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class.

All prior and concomitant medications will be presented in a patient listing.

6.2.6. Prior and Subsequent Anti-cancer Therapy

The prior and subsequent anti-cancer therapies, such as prior systemic anti-cancer therapy (Yes or No) prior radiotherapy (Yes or No), subsequent systemic anti-cancer therapy (Yes or No), and concomitant radiation therapy (Yes or No; Reason) will be summarized and listed. All verbatim terms collected of prior and subsequent anti-cancer therapy will be coded to Anatomical Therapeutic Classification (ATC) and PT using the WHO-DD Version Sep2017.

The prior anti-cancer therapy will summarize number of prior lines of therapy and the outcomes of those therapies. Subsequent anti-cancer therapy will summarize the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class. The data will be presented in a patient listing.

6.2.7. Efficacy Analyses

All the efficacy variables will be summarized using descriptive statistics by cycle or visit, with the supportive data provided in patient listings. Part 1 will be summarized using only descriptive statistics. For Part 2, in addition to the descriptive summary, the between treatment comparison (trilaciclib 240 mg/m^2 + topotecan 1.5 mg/m^2 vs placebo + topotecan), will be performed only for the primary and secondary endpoints outlined in Section 5.1.1-5.1.3. The comparisons between trilaciclib vs. placebo will be built into the multiplicity adjustment described in Section 6.2.7.1.3, the adjusted one-sided p-values will be reported and be the basis for the study drug efficacy conclusion and claim at the significance level of one-sided 0.10. However, for these comparisons, all statistical tests will be conducted at a two-sided .20 alpha level unless otherwise specified. Where appropriate, model-based point estimates, together with their two-sided 80% CIs will be presented along with the two-sided p-value for the test unless otherwise specified. Graphical presentation of efficacy results will be appropriately performed as needed.

Unless otherwise specified, all analyses for the efficacy endpoints will be conducted for the treatment period which is defined to be between the start of cycle for Cycle 1 and the end of the last cycle.

6.2.7.1. Primary and Key Secondary Efficacy Analyses

6.2.7.1.1. Primary Efficacy Analyses

The primary efficacy endpoint, occurrence of SVN, is a binary response variable (Yes, No). It will be summarized using descriptive statistics by treatment group and will be analyzed to compare trilaciclib and placebo using modified Poisson regression (Zou, 2004) to account for the variable duration of the treatment period for each patient. The model will include baseline ANC as a covariate, the stratification factors of ECOG (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant) and treatment as a fixed effect. The logarithm transformation of number of cycles will be included as an offset variable in the modeling. The two-sided p-value, adjusted rate ratio (aRR) (trilaciclib vs placebo) and its 80% CIs will be presented.

For the other primary efficacy endpoint, DSN in Cycle 1 based on Strategy 1 in Section 5.1.1.2.1, a two-sided p-value will be calculated for the nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA will include study baseline ANC value as covariate, stratification factors of ECOG (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant), and treatment as a fixed effect. Along with the descriptive statistics, the mean difference and Hodges-Lehmann estimate of median difference between the two treatment groups, together with its 80% CIs will be provided.

Additionally, DSN for each cycle will be presented using descriptive statistics.

6.2.7.1.2. Key Secondary Efficacy Analyses

Occurrence of RBC transfusions on/after 5 weeks on study is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1 except baseline HGB will be used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. An additional sensitivity analysis will look all transfusions during the treatment period, and all transfusions with a subset of subjects completing at least 1 cycle.

Occurrence of GCSF administration is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1.

All-cause dose reductions will be analyzed to compare trilaciclib and placebo using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of ECOG (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant), and treatment as a fixed effect. The logarithm transformation of number of cycles will be included as an offset variable in the modeling. The two-sided p-value, aRR (trilaciclib vs placebo) and its 80% CIs will be presented.

The total number of all-cause dose reductions will be summarized descriptively, along with the number of cycles, and the event rate per cycle (calculated as the total number of events/total number of cycles). The cumulative incidence of events during the treatment period will be summarized by cycle.

Occurrence of platelet transfusion is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1 except baseline platelet count will be used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset

will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles.

6.2.7.1.3. Key Secondary OS Analysis

OS will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated. It will be based on the ITT analysis set. The supportive data listings will also be provided.

In addition to the quartile summary from Kaplan-Meier method, Kaplan-Meier estimates will be provided for the survival rates at 3, 6, 9, and 12 months along with their 95% CIs. Additionally, a comparison will be conducted between trilaciclib and placebo. The two-sided p-value from a Cox proportional hazard model will be presented, the model includes treatment and stratification factors as fixed effects. The HR between the two treatment groups, together with its 80% CIs will be presented.

6.2.7.1.4. Multiplicity Adjustments

The clinical trial evaluates the objectives defined in terms of the comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group to placebo + topotecan group on the primary and key secondary myelosuppression efficacy endpoints in Sections 5.1.1 and 5.1.2. The resulting multiplicity problem include the following six hypotheses of no effect:

- Hypothesis H_1. Comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group versus placebo + topotecan group for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H_2. Comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group versus placebo + topotecan group for occurrence of severe (Grade 4) neutropenia.
- Hypothesis H_3. Comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group versus placebo + topotecan group for all-cause dose reductions in the MAHE composite.
- Hypothesis H_4. Comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group versus placebo + topotecan group for occurrence of RBC transfusions on/after Week 5 on study.
- Hypothesis H_5. Comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group versus placebo + topotecan group for occurrence of G-CSF administration.
- Hypothesis H_6.Comparison of Trilaciclib + Topotecan 1.5 mg/m^2 group versus placebo + topotecan group for occurrence of platelet transfusions.

A Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the multiple null hypotheses in the strong sense at a 1-sided α=0.10 level. The one-sided p-values for these comparisons will be used for the multiple test procedure, and the raw and adjusted 1-sided p-values will be provided in the summary.

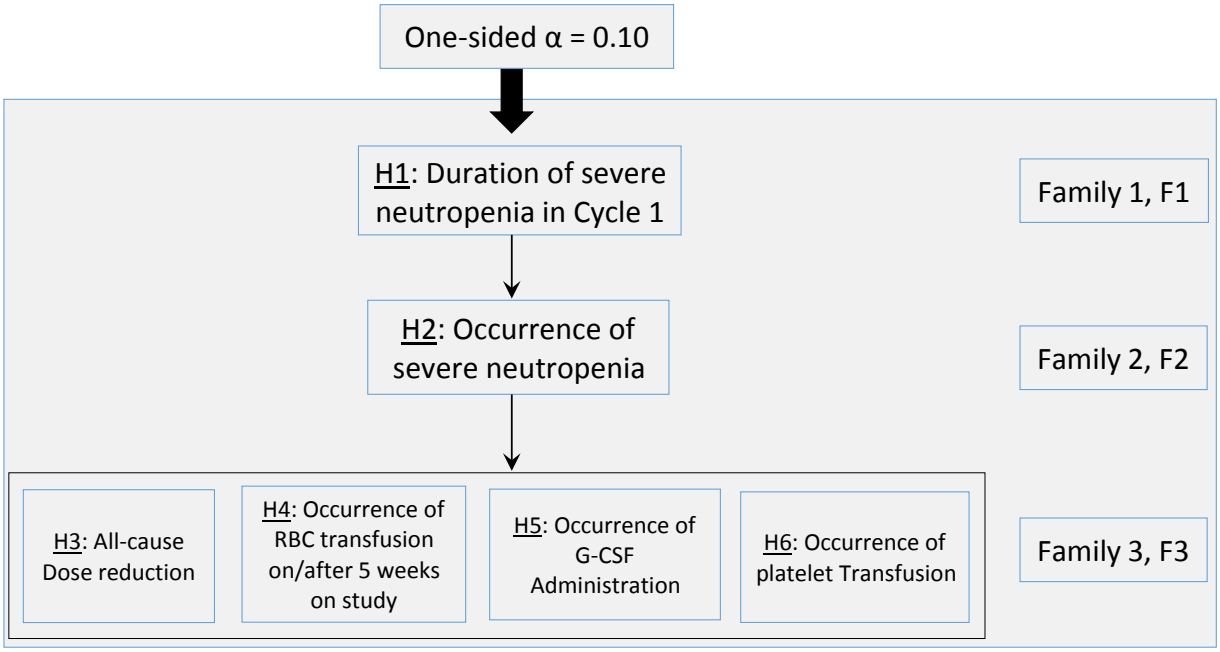
Gatekeeping procedure with logical restrictions

A Hochberg-based gatekeeping procedure satisfies the positive dependence condition given the 1-sided setting. The procedure is built using the mixture methodology developed in Dmitrienko and Tamhane (2011) and accounts for the logical restrictions among the 12 hypotheses displayed in Figure 6 by performing multiplicity adjustments in three steps. The logical restrictions can be

achieved by defining the parallel set and serial set for each individual hypothesis based the tree-structured procedure introduced by Dmitrienko et al (2007).

- Step 1. The Group 3 versus Group 1 comparisons for Family 1 (hypothesis H_1) is performed using a truncated version of the Hochberg procedure. The truncation parameter γ is set to 0.
- Step 2. The Group 3 versus Group 1 comparisons for Family 2 (hypothesis H_2) is performed using a truncated version of the Hochberg procedure if H_1 is significant in Step 1. The truncation parameter γ is set to 0.
- Step 3. The Group 3 versus Group 1 comparisons for Family 3 (hypotheses H_3, H_4, H_5, and H_6) are performed using the regular Hochberg test if H_2 is significant in Step 2.

Figure 6 Graphical Display of the Hochberg-based Gatekeeping Procedure



The logical restrictions in the Step 1 and Step 2 contain only one single hypothesis, and the Step 3 has four hypotheses H_3, H_4, H_5, and H_6 though the testing procedure can be broadly considered as a fixed sequence procedure, its implementation can be performed through the framework of Hochberg-based gatekeeping procedure as described in detail below.

The regular Hochberg test is defined in Dmitrienko et al. (2009) and the truncated Hochberg test is defined in Dmitrienko, Tamhane and Wiens (2008). The decision rules used in the regular and truncated Hochberg tests will be detailed in the following. In general terms, the truncated version of the Hochberg test is defined as a convex combination of the regular Hochberg and Bonferroni tests. An important parameter of the truncated Hochberg test is the truncation parameter γ which ranges between 0 and 1. If the truncation parameter γ is set to 0, the truncated Hochberg test simplifies to the Bonferroni test. On the other hand, if the truncation parameter γ is set to 1, the truncated Hochberg test is identical to the regular Hochberg test. The truncated Hochberg test satisfies the separability condition (Dmitrienko, Tamhane and Wiens, 2008) if the truncation parameter γ is strictly less than 1. This condition ensures that in each step of the testing algorithm the error rate can be transferred to the next step provided at least one Trilaciclib + Topotecan 1.5

mg/m^2 group versus placebo + topotecan group comparison is significant in the current step without inflating the overall type I error rate (Huque, 2016; FDA, 2017).

Testing algorithm

This section describes the implementation of the Hochberg-based gatekeeping procedure. The testing algorithm relies on the general approach to defining multistage gatekeeping procedures based on mixtures of multiple tests proposed in Dmitrienko and Tamhane (2011).

Decision rules

The aforementioned 6 hypotheses are grouped into 3 families:

- Family 1 (F_1) includes the hypotheses H_1.
- Family 2 (F_2) includes the hypothesis H_2.
- Family 3 (F_3) includes the hypotheses H_3, H_4, H_5, and H_6.

Using more compact notation, the families are defined as follows:

$$F_1 = \{H_i, i \in N_1\},\ F_2 = \{H_i, i \in N_2\},\ F_3 = \{H_i, i \in N_3\}.$$

where the index sets are defined as $N_1 = \{1\},\ N_2 = \{2\},\ N_3 = \{3, 4, 5, 6\}$. Let t_i and p_i denote the test statistic and 1-sided p-values associated with the hypotheses, respectively. Let α denote the global familywise error rate, i.e., one-sided $\alpha = 0.10$.

Consider the closed family associated with Families 1, 2 and 3, i.e., a family of all non-empty intersections of the twelve hypotheses. Each intersection will be identified by an index set

$$I \subseteq N\ = \{1, \ldots, 6\}$$

(note that the empty set is excluded). For example, the index vector $I = \{1, 2, 5\}$ corresponds to the intersection of the hypotheses H_1, H_2, and H_5.

To construct the Hochberg-based gatekeeping procedure that controls the global familywise error rate in the strong sense at an α level, an α-level test needs to be defined for each intersection in the closed family. The multiple test and associated p-value for an intersection are computed in two steps.

Step 1: Define *p*-values for subset intersections

Consider an intersection corresponding to the index set $I \subseteq N$ and define the index sets $I_k = I \cap N_k$, $k = 1, 2, 3$. The p-values for the index sets I_1, I_2, and I_3 are computed as follows:

Let n_1 denote the number of hypotheses included in I_1 and let $m_1 = n_1$. If $n_1 > 0$, the truncated Hochbergp-value is defined using the ordered p-values associated with the hypotheses included in the index set I_1, denoted by

$$p_{1(1)} \leq \cdots \leq p_{1(m_1)}$$

The truncated Hochberg p-value for the index set I_1 is given by

$$p(I_1) = \min_{i=1,\cdots,m_1} \frac{p_{1(i)}}{\frac{\gamma_1}{m_1 - i + 1} + (1 - \gamma_1)}$$

Here γ_1 is the pre-specified truncation parameter in Family 1. Choosing a larger value of γ_1 improves the power of comparisons in Family 1, and γ_1 is set to 0.

Further, let n_2 denote the number of hypotheses included in the index set I_2. If $n_2 > 0$, consider the hypotheses in the index set I_2 and remove the hypotheses that are not consistent with the logical restrictions defined in Figure 6. Let m_2 denote the number of hypotheses remaining in the index set I_2 after this logical restriction operation. If $m_2 > 0$, let

$$p_{2(1)} \leq \cdots \leq p_{2(m_2)}$$

denote the ordered p-values for the hypotheses remaining in the index set I_2. The truncated Hochberg p-value for I_2 is given by

$$p(I_2) = \min_{i=1,\cdots,m_2} \frac{p_{2(i)}}{\frac{\gamma_2}{m_2 - i + 1} + (1 - \gamma_1)}$$

where γ_2 is the pre-specified truncation parameter in Family 2, which plays the same role as γ_1 in Family 1, and γ_2 is set to 0.

Finally, let n_3 denote the number of hypotheses included in I_3. If $n_3 > 0$, remove the hypotheses that are not consistent with the logical restrictions defined in Figure 6. Let m_3 denote the number of hypotheses remaining in the index set I_3 after this logical restriction operation. If $m_3 > 0$, let

$$p_{3(1)} \leq \cdots \leq p_{3(m_3)}$$

denote the ordered p-values for the hypotheses remaining in the index set I_3. The Hochberg p-value for I_3 is given by

$$p(I_3) = \min_{i=1,\cdots,m_3} \frac{p_{3(i)}}{\frac{1}{m_3 - i + 1}}$$

Step 2: Define overall p-value

The overall p-value for the intersection corresponding to the index set I is computed by combining the p-values associated with the index sets I_1, I_2, and I_3. Consider the following three scenarios:

- If $n_1 > 0$, the overall p-value is found using the following mixing function:

$$p(I) = \min\left(\frac{p(I_1)}{b_1}, \frac{p(I_2)}{b_2}, \frac{p(I_3)}{b_3}\right)$$

where $b_1 = 1,\ b_2 = b_1(1 - f_1),\ b_3 = b_2(1 - f_2)$ and f_1 and f_2 are computed based on the error rate functions of the truncated Hochberg tests used in Families 1 and 2. These quantities are defined below.

- If $n_1 = 0$ and $n_2 > 0$, the overall p-value is given by

$$p(I) = \min\left(\frac{p(I_2)}{b_2}, \frac{p(I_3)}{b_3}\right)$$

where $b_2 = 1,\ b_3 = b_2(1 - f_2)$.

- If $n_1 = 0, n_2 = 0$ and $n_3 > 0$, the overall p-value is given by

$$p(I) = \frac{p(I_3)}{b_3}$$

where $b_3 = 1$.

The error rate function of the truncated Hochberg test with the truncation parameter γ_k for testing an intersection corresponding to the index set I_k, $k = 1, 2$, is defined as

$$e_k(I_k) = P[p(I_k) \leq \alpha]$$

and $f_k = e_k(I_k)/\alpha$, $k = 1, 2$. It is shown in Brechenmacher et al. (2011) that

$$e_k(I_k) = [\gamma_k + (1 - \gamma_k)|I_k|/n_k]\alpha$$

if the index set I_k is non-empty and $e_k(I_k) = 0$ the index set I_k is empty. Here $|I_k|$ denotes the number of hypotheses included in the index set I_k.

As shown in Dmitrienko and Tamhane (2011), the resulting test for the intersection corresponding to the index set I is an α-level test. This implies that the Hochberg-based gatekeeping procedure controls the global familywise error rate in the strong sense at a one-sided $\alpha = 0.10$.

Multiplicity-adjusted p-values

Multiplicity-adjusted p-values for the Hochberg-based gatekeeping procedure are computed using the closure principle. For each hypothesis, the adjusted p-value is defined as the maximum over the p-values associated with the intersections in the closed family that include the hypothesis of interest. For example, the adjusted p-value for H_2 is the maximum over the p-values for intersections containing H_2. The calculations are performed using the decision matrix algorithm, see Dmitrienko and Tamhane (2011).

Regular and truncated Hochberg tests

Consider a general problem of testing m null hypotheses denoted by $H_1, \ldots, H_m$. Let $p_1, \ldots, p_m$ denote the associated raw p-values. Further, let $p_{(1)} < \cdots < p_{(m)}$ denote the ordered p-values and $H_{(1)} < \cdots < H_{(m)}$ denote the hypotheses corresponding to the ordered p-values.

The regular Hochberg test is based on the following testing algorithm:

- Step 1: If $p_{(m)} > \alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.
- Step $i = 2, \ldots, m - 1$: If $p_{(m-i+1)} > \alpha/i$, accept $H_{(m-i+1)}$ and go to Step $i + 1$, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$.

The truncated Hochberg test with the truncation parameter γ is based on the following testing algorithm:

- Step 1: If $p_{(m)} > [\gamma + (1 - \gamma)/m]\alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.

- Step $i = 2, \ldots, m-1$: If $p_{(m-i+1)} > [\gamma/i + (1-\gamma)/m]\alpha$, accept $H_{(m-i+1)}$ and go to Step $i+1$, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$

6.2.7.1.5. Robustness of Primary and Key Secondary Efficacy Analyses

A binary response variable (Yes, No) will be analyzed to compare trilaciclib and placebo using stratum-adjusted method to account for the baseline ECOG status (0 to 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant) as the stratification factors. The adjusted proportion difference (trilaciclib vs placebo) and its 80% CIs will be calculated using Cochran-Mantel-Haenszel (CMH) weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method. Additionally, three sets of sensitivity analysis will be conducted to evaluate the robustness of the results from primary or key secondary analyses for a binary response variable (Yes, No).

(i) For patients who die during the treatment period without experiencing an event, Yes will be assigned to the variable.

(ii) After the imputation from (i), a worst-comparison analysis will be done to establish a stringent boundary of the treatment effect. Patients who die during the treatment period will still be set to Yes, and patients who discontinue the study prior to the September 28, 2018 data cutoff date without experiencing an event will then be imputed. If the patient is from the placebo group, No will be assigned to the variables, Yes will be assigned to the trilaciclib groups.

(iii) After the imputation from (i), a tipping-point analysis (Yan et al,. 2009) will be performed by assigning the response to the variable for patients who discontinue the study early during the treatment period without experiencing an event.

The tipping-point analysis assumes all possible combinations of numbers of Yes and No for the missing responses (defined as patients without an event who have discontinued the study prior to the September 28, 2018 data cutoff date) in the trilaciclib and placebo groups. For example, let n_t be the number of randomized trilaciclib patients with missing response and n_p be the number of randomized placebo patients with missing responses. For the trilaciclib patients with missing values, there are $n_t + 1$ possible assumptions for number of No (i.e. 0, 1, 2, …, to n_t); for the placebo patients with missing values, there are $n_p + 1$ possible assumptions for number of No. Therefore, there are total of $(n_t + 1) \times (n_p + 1)$ possible combination of assumptions for number of No and Yes for the trilaciclib and placebo patients with missing responses. The un-stratified exact CMH method will be performed on the available responses with each of these $(n_t + 1) \times (n_p + 1)$ assumptions and will be summarized. A figure will be presented with points representing each possible combination where the significant p-value 'tips' to greater than a one-sided 0.10, which would represent a change in the study conclusions. Clinical justification will be provided to evaluate whether the assumption is plausible.

A waterfall plot showing the number of cycles with SVN will be presented.

DSN for each cycle will be presented using descriptive statistics. The primary analysis on DSN defined by Strategy 1 (refer to Section 5.1.1.2.1) will be repeated on DSN defined by Strategy 3 (refer to Section 5.1.1.2.3).

Each of the analyses will be repeated using two additional distinct data sets to evaluate the confounding effect of GCSF administration: inclusion of only those patients or cycles who had concurrent GCSF administration; and inclusion of only those patients or cycles who did NOT have concurrent GCSF administration. The "with" and "without" GCSF analyses are subsets of the total number of patients or cycles.

DSN, Strategy 2 (refer to Section 5.1.1.2.2) will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated. Additionally, DSN for each cycle will be presented using descriptive statistics.

In addition to the summary from Kaplan-Meier method, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the stratification factors of ECOG (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant). The hazard ratio (HR) between the two treatments (trilaciclib vs placebo), together with its 80% CIs will be calculated from a Cox proportional hazard model in which treatment and the stratification factors will be included as fixed effects.

For RBC transfusions, subsets of subjects with baseline HGB <9 g/L and ≥9 g/L will be provided, as well as a summary of the number of units transfused.

The primary and key secondary efficacy endpoints are based on the ITT analysis set, and the analysis will be repeated for the mITT analysis set and PP analysis set.

6.2.7.2. Supportive Efficacy Analyses

6.2.7.2.1. Analyses of Total Number of MAHE

The total number of MAHE in Section 5.1.3.1 will be analyzed to compare trilaciclib and placebo using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of ECOG (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant), and treatment as a fixed effect. The logarithm transformation of duration of treatment period divided by 7 (i.e. week) will be included as an offset variable in the modeling. The two-sided p-value, aRR (trilaciclib vs placebo) and its 80% CIs will be presented.

The total number of MAHE will be summarized descriptively, along with the weeks of treatment duration, and the event rate per week (calculated as the total number of events/duration of treatment period divided by 7 [i.e. week]). The cumulative incidence of events during the treatment period will be summarized and presented graphically in three-week intervals.

The total number of individual MAHE components (specified in Table 4) will be summarized similarly, except that DSN > 5 days will be summarized cumulatively by cycle instead of three-week intervals, and the offset will be the logarithm transformation of number of cycles instead of duration of treatment period.

Time-to-first MAHE endpoints (overall and individually) in Section 5.1.3.1 will be summarized similar to DSN, Strategy 2 as described in Section 6.2.7.1.5. A graphical display of cumulative incidence will also be presented.

An event chart of the treatment period will also be included, with horizontal bars for each subject's cycle length and time on the x-axis, with points plotted for each of the MAHE components.

For the time (days) to first occurrence of a MAHE event, a graphical display of cumulative incidence will be presented.

6.2.7.2.2. Analyses of Objective Response

The patients in each category of TPR according to the investigator tumor assessment (CR, PR, SD, PD, or NE) will be presented in a data listing. The number and percentage of patients in each category of BOR (Confirmed CR, Confirmed PR, SD, PD, or NE), ORR, $ORR_{UNCONFIRMED}$ and CBR according to the investigator tumor assessment (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized. Detailed information of deriving tumor relevant responses is provided in Section 5.1.3.2.4.

Similar analyses will be repeated based on the derived responses according to the RECIST Version 1.1.

Estimates of response rate, along with its associated exact 95% two-sided CIs using Clopper-Pearson method will be computed for ORR and CBR within each treatment group.

The binary endpoint (Yes, No) of ORR for the two treatments (trilaciclib and placebo) will be analyzed to compare trilaciclib and placebo using stratum-adjusted method to account for the stratification factors of ECOG (0 or 1 vs. 2) and sensitivity to first-line treatment (sensitive or resistant). The adjusted proportion difference (trilaciclib vs placebo) and its 80% CIs will be calculated using CMH weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method.

The analyses are based on the response evaluable analysis set. The supportive data listings will also be provided.

Subsets based on subjects with and without dose reductions will also be included.

A waterfall plot showing the best % change in target lesion sum will also be included.

6.2.7.2.3. Analyses of DOR and PFS

The analysis method as described in Section 6.2.7.1.3 for OS will be applied to PFS (derived, and derived with clinical progression) and DOR (investigator and derived), except DOR will exclude the Kaplan-Meier estimates for the survival rates at 3, 6, 9, and 12 months as well as the Cox proportional hazard model.

Spider plot by treatment group of % change in target lesion from baseline for each subject over time will be included based on derived assessments. Points will be included for best overall response (if CR or PR), new lesions, and end of treatment.

An event chart of the treatment period will also be included, with horizontal bars for each subject's cycle length and time on the x-axis, with points plotted for start and end of DOR.

For DOR, the analysis is based on the response evaluable analysis set; for PFS the analysis will be based on the ITT. The supportive data listings will also be provided. For the PFS, the derived

endpoint based on only radiologic progression will be considered as the primary, and the derived endpoint based on both radiologic and clinical progression will be considered as supportive.

6.2.7.2.4. Analyses of Hematology Lab Values

For the endpoints specified in Sections 5.1.3.4 and 5.1.3.5, in addition to descriptive statistics summary, appropriate graphical display will be provided to facilitate evaluation of trends in the change in a given variable over time. Moreover, each of the ANC change over time analysis (i.e. observed value at windowed visit and cycle nadir) specified above will be done using three distinct data sets to evaluate the confounding effect of GCSF administration: all patients or cycles regardless of GCSF administration; inclusion of only those patients or cycles who had concurrent GCSF administration; and inclusion of only those patients or cycles who did NOT have concurrent GCSF administration. The "with" and "without" GCSF analyses are subsets of the total patient or cycles.

Figures of mean and 95% CI over time will be provided for ANC (with GCSF subsets also), platelet counts, HGB, change from baseline HGB, and ALC. Additionally, jitter scatter plots will be provided for mean and 95% CI by cycle for ANC nadir (with GCSF subsets also).

A Radar plot of grade 3/4 laboratory abnormalities during the treatment period, and during the first cycle will be presented.

6.2.7.2.5. Analyses of Other Binary Efficacy Endpoints

The following binary response variables (Yes, No) will be analyzed using the same method for occurrence of SVN except baseline ANC will not be a covariate in the modified Poisson model. See Section 6.2.7.1.1:

- Occurrence of a Grade 3 or 4 hematologic toxicity during the treatment period (refer to Section 5.1.3.3);
- Occurrence of an ESA administration during the treatment period (refer to Section 5.1.3.6);
- Occurrence of an IV antibiotic administration during the treatment period (refer to Section 5.1.3.7); The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally, total number of IV antibiotic administrations will be summarized descriptively.
- Occurrence of an infection SAE during the treatment period (refer to Section 5.1.3.8); The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally, total number of infection SAEs will be summarized descriptively.
- Occurrence of a pulmonary infection SAE during the treatment period (refer to Section 5.1.3.9). The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally, total number of pulmonary infection SAEs will be summarized descriptively.
- Occurrence of a Grade 4 and Grade 3 or 4 thrombocytopenia (laboratory values) during the treatment period (refer to Section 405.1.3.11);

6.2.7.2.6. Analysis of Myelosuppression Endpoints with All data up to End of Cycle 4

The analyses outlined in Section 5.1.3.12 will be analyzed using the same methods using the same methods as the analogous primary, secondary, and supportive efficacy analyses, except they will only use data up through the end of Cycle 4.

For Occurrence of severe (Grade 4) neutropenia see Section 6.2.7.1.1; For Occurrence of RBC transfusions on/after week 5 of study, Occurrence of GCSF administrations, Occurrence of platelet transfusions, and Occurrence of RBC transfusions during the first 4 cycles see Section 6.2.7.1.2.

For Total number of MAHE, Number of all-cause hospitalizations, Number of cycles with all-cause dose reductions, Number of febrile neutropenia, Number of cycles with prolonged severe (Grade 4) neutropenia (duration > 5 days), Number of RBC transfusions on/after 5 weeks, Number of platelet transfusions, and Number of RBC transfusions during the first 4 cycles see Sections 6.2.7.1.2 and 6.2.7.2.1.

For Occurrence of Grade 3 and 4 hematologic toxicities see Section 6.2.7.2.5.

6.2.7.3. Exploratory Efficacy Analyses

For all three exploratory endpoints listed in Sections 5.1.4.2, 5.1.4.3, and 5.1.4.4, the data will only be summarized using descriptive statistics, hence, the general rules outlined in Section 6.1.1 will be followed. Moreover, the supportive data listings will be provided.

6.2.8. Safety Analyses

All safety analyses will be based on the safety analysis set, as defined in Section 3.1.2. Descriptive statistics will be used to summarize the safety outcomes. The continuous safety variables will be summarized at each visit including end of each cycle (the last non-missing assessment during the cycle), end of treatment (the last non-missing assessment during the treatment period), and end of study (the last non-missing assessment during the whole study), if applicable. No inferential analyses of safety data are planned unless otherwise specified.

6.2.8.1. Chemotherapy Exposure and Compliance Analyses

Duration on treatment and number of cycles will be summarized by treatment. Dose intensity for each study drug (topotecan or trilaciclib/placebo) will be summarized for patients in Part 1; only trilaciclib/placebo will be summarized for Part 2. Dose modifications will be summarized for each study drug (topotecan or trilaciclib/placebo). For each study drug, the dosing endpoints described in Section 5.2.1 will be summarized by treatment. This includes the following:

- Number of cycles received;
- Number of missed doses;
- Number of dose reductions;
- Number of dose interruptions;
- Number of patients with missed dose and its reason;
- Number of patients with dose reductions and reason;
- Number of patients with dose interruptions.
- Number of doses

The number of cycles delayed, the number and percentage of patients experiencing a treatment cycle delay, and reason for cycle delay will be summarized by treatment. The study dosing records and the derived dosing endpoints will be listed.

6.2.8.2. Adverse Events

Number and incidence rates of AEs will be summarized by SOC and/or PT for the following categories of TEAEs: all AEs, SAEs, AEs leading to death, and AEs leading to study drug (topotecan or trilaciclib/placebo) discontinuation or study withdrawal. Patients with more than one occurrence of the same SOC (PT) will be counted only once within the SOC (PT) categorization.

AEs will also be summarized similarly by CTCAE grade and relationship to any study drug (topotecan or trilaciclib/placebo), and by relationship to each drug. Should a patient experience more than one occurrence of the same SOC (PT), the patient's worst occurrence (worst grade/most related causality) will be retained in the tabulation.

All AEs, including AEs that started prior to the study medication, will be presented in patient listings. In addition, separate listings of all SAEs, AEs leading to death, drug-related AEs, AEs leading to study drug (topotecan or trilaciclib/placebo) discontinuation or study withdrawal, and DLTs will be provided.

The criteria for identifying infusion related reaction AEs or hematologic toxicity AEs are described in Section 5.2.1. A summary table showing incidence of AEs related to infusion and related to hematologic toxicity will be presented along with its supportive data listing.

6.2.8.3. Laboratory Evaluations

For hematology and clinical chemistry labs the observed values and change from baseline will be summarized for each visit during the treatment period using descriptive statistics.

Toxicities for clinical labs will be characterized according to CTCAE, Version 4.03 (Table A-1 of Appendix when possible), and the frequency and percentage of patients with each CTCAE grade for each visit during the treatment period will be described. Moreover, any occurrence of grade 3 or grade 4 during the treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Listings of all laboratory data, normal reference ranges, and CTCAE grades (when possible) will be provided.

6.2.8.4. Vital Signs

For vital sign parameters (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature, and Weight) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 13) during the treatment period will be presented. A listing of all vital sign data will be provided.

6.2.8.5. Performance Status

Descriptive statistics will be presented for ECOG score for the observed values and change from baseline. A listing of ECOG score for all patients will be provided.

6.2.8.6. Physical Examination

A listing of physical examination findings for all patients will be provided (where available).

6.2.8.7. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline. A listing of all ECG data will be provided.

The criteria for potentially clinically significant findings are defined in Table 15. The frequency and percentage of patients with any potentially clinically significant findings during the treatment period will be presented. The supportive data will be provided in patient data listings.

6.2.9. Subgroup Analyses

The MAHE, OS, and PFS will be examined in the following subgroups:

- Age group (ages <65; ≥65).
- Gender (Male; Female).
- ECOG performance status (0-1; 2).
- Sensitivity to first treatment (Sensitive; Resistant).
- Race (Caucasian; non-Caucasian).
- Region (US; Ex-US).
- Baseline LDH (≤ ULN; > ULN).

Descriptive statistics by treatment group will be presented for each subgroup of patients.

Additional subgroups or endpoints may be identified and explored.

6.2.10. Pharmacokinetic Analysis

The PK analysis for a subset of patients will be documented separately and is not covered in this SAP.

6.2.11. Assess Genetic and/or Expression (RNA/Protein) Biomarkers in Tumors and Blood

A detailed description of the biomarker analysis plan will be documented separately. In general, as data permits, the analyses may include, but not be limited to:

1. SCLC tumor samples may be assessed for markers of CDK 4/6 dependence and independence (including but not limited to PD-L1, PD-1, and others) as defined by IHC or qRT-PCR on biological/clinical endpoints.
2. SCLC tumor samples may be assessed for markers to potentially predict sensitivity to trilaciclib treatment.
3. Peripheral blood samples may be assessed for biomarkers examining the role of trilaciclib in the preservation of hematopoietic and immune populations during chemotherapy treatment

4. Peripheral blood samples may be assessed for biomarkers examining the role of trilaciclib in anti-tumor immunity

6.2.12. Planned Analysis

The final myelosuppression analysis will be conducted after all patients have had the opportunity to receive at least 12 weeks of treatment. All study data collected through the time of the final myelosuppression analysis data cut will be included. This includes, but is not limited to the final myelosuppression analysis, interim ORR analysis based on investigator assessment, and interim PFS/OS analysis.

The time of analysis with at least 80% of patients having experienced a progression will be considered to be final PFS analysis. Patients will be followed for survival until at least 70% of the patients have died, and a final OS analysis will be done then. Additional exploratory analyses of OS/PFS may between the final myelosuppression analysis and study completion. Reported results, with the exception of the myelosuppression analyses, will be cumulative in nature, including all data collected during the entire study; the myelosuppression analyses will be complete at the final analysis and no additional data will be expected.

7. CHANGE FROM THE PROTOCOL

The timing of the final analysis, analysis sets, and endpoints were updated based on scientific advice, regulatory guidance, and feedback on other trilaciclib studies. The endpoints and analyses listed below are based on the Statistics Section in the Protocol Amendment 5, dated 27 June 2018. The list displays the endpoints and analyses which are removed from the initial analysis and are therefore not described in the SAP.

Protocol Section 13.4.1 (Efficacy Endpoints):

- Hematologic kinetic endpoints:
    - Change and percent change in hematologic parameter values from predose for a particular cycle to the end of that cycle
    - Change and percent change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
    - Rate of change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
    - Change and percent change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Rate of change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Area under the curve in hematologic parameter values from predose for a particular cycle to the end of that cycle
    - Area under the curve in hematologic parameters from predose for a particular cycle to nadir for that cycle
    - Area under the curve in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Time to hematologic parameter value nadir by cycle
    - Time to return to predose hematologic parameter values by cycle
    - Proportion of patients with a return to predose hematologic parameter values by cycle
- Hematologic toxicity endpoints:
    - Proportion of patients with a hematologic toxicity recovery by cycle.
    - Time to hematologic toxicity recovery by cycle
- Exploratory efficacy endpoints:
    - Composite hematologic score
    - Composite efficacy score

Protocol Section 13.4.2.1 (Analysis of Hematologic Parameter Kinetic Endpoints)

- Additional tabulations for each cycle of treatment in maximum postnadir values.

- The tabulation of the changes and percent changes from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle values for each cycle of treatment.
- Analysis of covariance (ANCOVA) models on hematologic parameter kinetic endpoints
- Summarization of time to nadir.
- Descriptive statistics and ANCOVA of area under the curve (AUC) in hematologic parameters
- Repeated-measures model of AUC
- Summary of proportion of patients return to predose value for each cycle. calculation on incidence rate, adjusting for cumulative exposure
- Analysis of time to return to predose level for each cycle using Kaplan-Meier method.
- Analysis of Time to return to postnadir predose levels

Protocol Section 13.4.2.2 (Analysis of Hematologic Toxicity Endpoints)

- Calculation and analysis of incidence rate of hematologic toxicity, adjusting for cumulative exposure
- Calculation and analysis of toxicity rate relative to cumulative exposure (total number of toxicities divided by cumulative exposure).
- Recurrent events model estimating the incidence of Grade 3 or higher hematologic toxicities and testing for the difference between treatment groups.
- For each hematologic parameter and cycle, the shift summaries of the following:
    - From predose toxicity to maximum on treatment toxicity;
    - from predose toxicity to end of cycle toxicity;
    - from maximum postdose toxicity to end of cycle toxicity.

Protocol Section 13.4.2.4 (Other Efficacy Endpoints)

- The number and percent of infections summarized by maximum severity
- The infection rate: The number of infections occurring during the Treatment divided by cumulative exposure.

Protocol Section 13.6 (Exploratory Analyses)

- The relationship between hematologic toxicity rates and changes with study drug (topotecan or trilaciclib/placebo) exposure
- The association between composite endpoints and BOR, OS, and PFS
- The FACT-L and FACT-An analyses analysis in the section is not covered in the SAP

8. REFERENCES

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Table A-1 Clinical Laboratory Parameters CTCAE Criteria

Parameter	Grade				
	1	2	3	4	5
Albumin	<LLN – 3 g/dL; <LLN – 30 g/L	<3 – 2 g/dL; <30 – 20 g/L	<2 g/dL; <20 g/L	-	-
ALP	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
ALT	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
AST	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	-
Calcium (Hypercalcemia)	Corrected serum calcium of >ULN – 11.5 mg/dL; >ULN – 2.9 mmol/L	Corrected serum calcium of >11.5 – 12.5 mg/dL; >2.9 – 3.1 mmol/L	Corrected serum calcium of >12.5 – 13.5 mg/dL; >3.1 – 3.4 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L	-
Calcium (Hypocalcemia)	Corrected serum calcium of <LLN – 8.0 mg/dL; <LLN – 2.0 mmol/L	Corrected serum calcium of <8.0 – 7.0 mg/dL; <2.0 – 1.75 mmol/L	Corrected serum calcium of <7.0 – 6.0 mg/dL; <1.75 – 1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L	-
CK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	-
Creatinine	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	-
GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Glucose (Hyperglycemia)	Fasting glucose value >ULN – 160 mg/dL; Fasting glucose value >ULN – 8.9 mmol/L	Fasting glucose value >160 – 250 mg/dL; Fasting glucose value >8.9 – 13.9 mmol/L	Fasting glucose value >250 – 500 mg/dL; Fasting glucose value >13.9 – 27.8 mmol/L	Fasting glucose value >500 mg/dL; Fasting glucose value >27.8 mmol/L	-
Glucose (Hypoglycemia)	<LLN – 55 mg/dL; <LLN – 3.0 mmol/L	<55 – 40 mg/dL; <3.0 – 2.2 mmol/L	<40 – 30 mg/dL; <2.2 – 1.7 mmol/L mmol/L	<30 mg/dL; <1.7 mmol/L	-
Hemoglobin	<LLN – 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-	-
Potassium (Hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	-

Table A-1 Clinical Laboratory Parameters CTCAE Criteria					
	Grade				
Parameter	1	2	3	4	5
Potassium (Hypokalemia)	<LLN – 3.0 mmol/L	-	<3.0 – 2.5 mmol/L	<2.5 mmol/L	-
Lymphocyte	<LLN – 800/mm3; <LLN – 0.8 x 10e9 /L	<800 – 500/mm3; <0.8 – 0.5 x 10e9 /L	<500 – 200/mm3; <0.5 – 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
ANC	<LLN – 1500/mm3; <LLN – 1.5 x 10e9 /L	<1500 – 1000/mm3; <1.5 – 1.0 x 10e9 /L	<1000 – 500/mm3; <1.0 – 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Phosphates	<LLN – 2.5 mg/dL; <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL; <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL; 0.6 – 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L	-
Platelet Count	<LLN – 75,000/mm3; <LLN – 75.0 x 10e9 /L	<75,000 – 50,000/mm3; <75.0 – 50.0 x 10e9 /L	<50,000 – 25,000/mm3; <50.0 – 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Sodium (Hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	-
Sodium (Hyponatremia)	<LLN – 130 mmol/L	-	<130 – 120 mmol/L	<120 mmol/L	-
Urate	>ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L	-
White blood cell	<LLN – 3000/mm3; <LLN – 3.0 x 10e9 /L	<3000 – 2000/mm3; <3.0 – 2.0 x 10e9 /L	<2000 – 1000/mm3; <2.0 – 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-

LLN=lower limit of normal range; ULN=upper limit of normal range.