STATISTICAL ANALYSIS PLAN

Study Title:	Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Etoposide and Carboplatin 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:	G1T28-02
Phase:	Phase 1b/2a
Analysis Plan Version	Version 1.0
Version Date	14 February 2018

APPROVAL SIGNATURES

AUTHOR:

DocuSigned by:
Zack Scott
Signer Name: Zack Scott
Signing Reason: I am the author of this document
Signing Time: 14-Feb-2018 | 10:49 AM EST
B0732999AA74463F9272293C562B38A0

14-Feb-2018 | 10:49 A

Signature **Date**

Zack Scott, MS
Senior Biostatistician
Pharpoint Research

APPROVED BY:

DocuSigned by:
Yang Zhao
Signer Name: Zhao Yang
Signing Reason: I approve this document
Signing Time: 14-Feb-2018 | 12:57 PM EST
BD42D5FBFAF147428F4FD03BC5158CE7

14-Feb-2018 | 12:57

Signature **Date**

Zhao (Tony) Yang, PhD
Associate Director of Biostatistics
G1 Therapeutics Inc

DocuSigned by:
Shannon Morris
Signer Name: Shannon Morris
Signing Reason: I approve this document
Signing Time: 14-Feb-2018 | 13:57 PM EST
21D3F8A5CA8D4D238C3F7456578609D7

14-Feb-2018 | 13:57

Signature **Date**

Shannon Morris, M.D. PhD
VP, Clinical Development
G1 Therapeutics Inc

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under Curve
B-HCG	Beta Human Chorionic Gonadotropin
BICR	Blinded Independent Central Review
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
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	Electronic Case Report Form
EOI	End of Infusion
E/P	Etoposide and Carboplatin
E/P THERAPY	Etoposide and Carboplatin on Day 1 and Etoposide on Days 2 and 3 of 21-Day Cycles
ESA	Erythropoietin Stimulating Agent
EWB	Emotional Well-Being
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-AN	Functional Assessment of Cancer Therapy –Anemia
FACT-L	Functional Assessment of Cancer Therapy –Lung

Abbreviation	Term
FAS	Full Analysis Set
FWB	Functional Well-Being
G-CSF/GCSF	Granulocyte Colony-Stimulating Factor
HR	Hazard Ratio
ICH	International Conference on Harmonization
IV	Intravenous
LCS	Lung Cancer Subscale
LD	Longest Diameter
LDH	Lactate Dehydrogenase
MAHE	Major Adverse Hematologic Event
MEDDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NADIR	The Lowest Point
NE	Not Evaluable
NLR	Neutrophil-Lymphocyte Ratio
NTL	Non-Target Lesion
OC	Observed Case
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PLR	Platelet-Lymphocyte Ratio
PP	Per Protocol
PR	Partial Response
PRO	Patient-Reported Outcome
PT	Preferred Term
PWB	Physical Well-Being
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
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SWB	Social/Family Well-Being
TEAE	Treatment-Emergent AE
TL	Target Lesion
TLFs	Tables, Listings, and Figures

Abbreviation	Term
TOI	Trial Outcome Index
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 following the completion of Study G1T28-02, Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Extensive-Stage SCLC Receiving Etoposide and Carboplatin Chemotherapy. The SAP is based on the G1T28-02 Protocol Version 8, dated 15 September 2016.

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).

2. STUDY DETAILS

2.1. Study Objectives

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

Table 1 G1T28-02: Study Objectives

	Phase 1b Dose-Finding Portion of Part 1	Phase 2a Expansion Portion of Part 1	Phase 2a Part 2
Primary Objectives			
Assess the DLTs and define the Phase 2 dose of G1T28 administered with E/P therapy	X		
Assess the safety and tolerability of G1T28 administered with E/P therapy	X	X	X
Secondary Objectives			
Assess the PK profile of G1T28	X		
Assess the PK profile of etoposide and carboplatin when administered with G1T28	X		
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of G1T28 administered with E/P therapy	X	X	X
Assess the incidence of febrile neutropenia	X	X	X
Assess the incidence of infections	X	X	X
Assess the utilization of RBC and platelet transfusions	X	X	X
Assess the utilization of hematopoietic growth factors	X	X	X
Assess the utilization of systemic antibiotics	X	X	X
Assess the incidence of chemotherapy dose reductions and dose interruptions overall	X	X	X
Assess the incidence of Grade 2 or greater nephrotoxicity	X	X	X
Assess tumor response based on RECIST, Version 1.1	X	X	X
Assess PFS and overall survival	X	X	X
Exploratory Objectives			
Assess the incidence of mucositis	X	X	X
Assess the incidence of alopecia	X	X	X
Assess the incidence of fatigue	X	X	X
Assess patient-reported QOL	X	X	X
Assess immunologic markers			X

DLT = dose-limiting toxicity; E/P therapy = etoposide + carboplatin on Day 1 and etoposide on Days 2 and 3 of 21-day cycles; PFS = progression-free survival; PK = pharmacokinetic; QOL = quality of life; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

2.2. Study Design

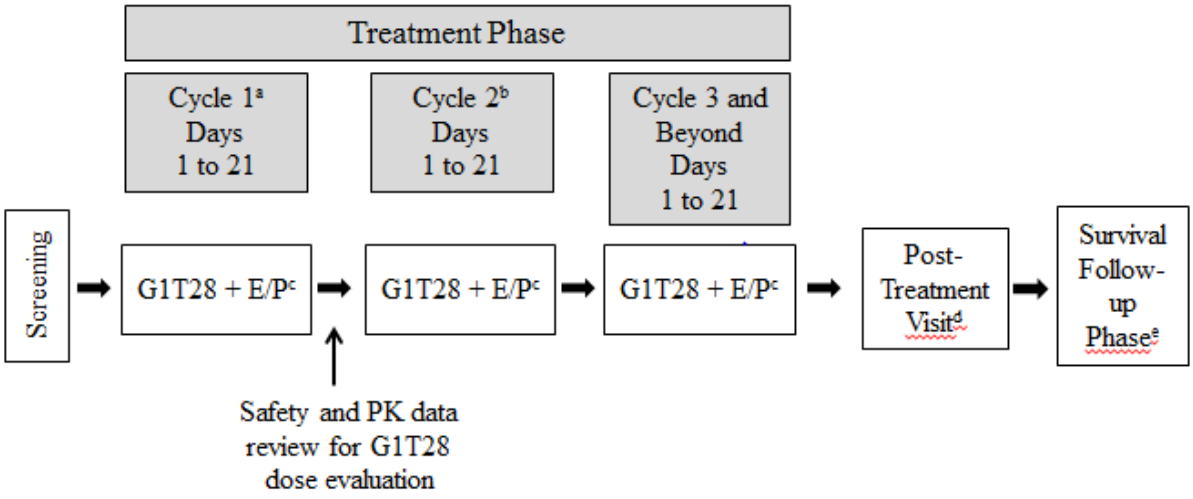
This is a randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2a study of the safety and PK of G1T28 in combination with E/P therapy for patients with newly diagnosed extensive-stage SCLC. The study consists of 2 parts: Part 1 will be a limited Phase 1b, open-label, dose-finding portion followed by a Phase 2a, open-label, expansion portion in up to 18 patients at the selected dose to be used in Part 2. Prior to initiating Part 2, up to a total of 24 patients will be enrolled at the chosen Part 2 dose (6 patients in the dose-finding portion of Part 1 and up to 18 patients in the Phase 2a, open-label, expansion portion of Part 1). Part 2 will consist

of a randomized, double-blind cohort (70 patients will be randomly assigned to G1T28 administered IV with E/P therapy or placebo administered IV with E/P therapy). All parts of the study 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

Part 1 starts with a dose finding portion which will be followed by an expansion portion. The goal of the Phase 1b dose-finding portion of Part 1 is to assess the safety, including dose-limiting toxicities (DLTs) and PK of G1T28 administered at a starting dose of 200 mg/m^2 once daily on Days 1 to 3 of E/P therapy. DLTs are defined in Protocol section 6.1.1.1. The schema of Part 1 is shown in Figure 1.

Figure 1 Study Schema: Part 1



E/P = etoposide + carboplatin

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 G1T28 + E/P will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). 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 G1T28 will be administered prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles

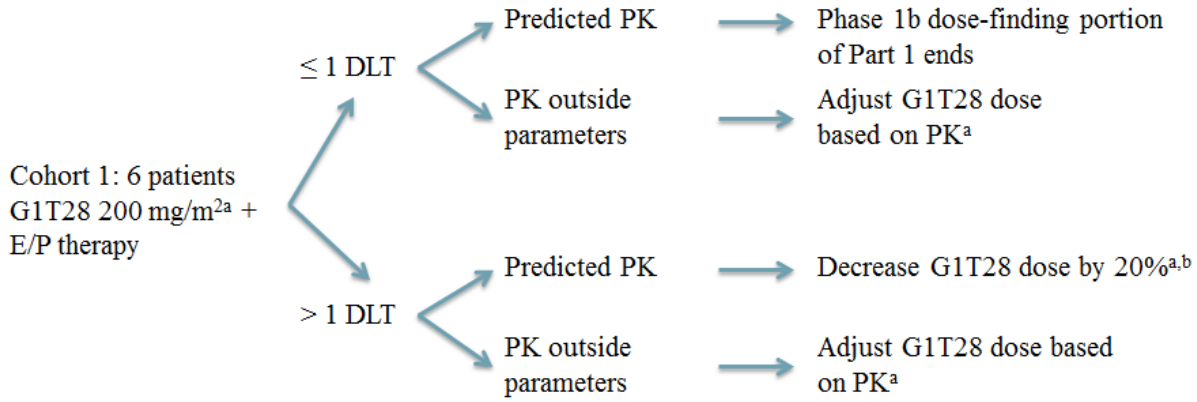
d Patients will return to the study center for a Post-Treatment Visit at 30 ± 3 days after the last dose of study drug.

e The Survival Follow-up Phase will continue until at least 50% of the patients randomized to Part 2 of the study have died.

Part 1b Dose Finding

For the dose finding portion, it is an open-label, ascending dose trial of G1T28 administered at a dose of 200 mg/m^2 intravenous (IV) once daily on Days 1 to 3 of E/P therapy to patients with unequivocally confirmed newly diagnosed extensive-stage SCLC. Enrollment in the dose finding portion is planned to include up to 22 male and female patients (depending on the number of dose escalation cohorts required, assuming up to 3 cohorts) at least 18 years old to evaluate safety, including DLTs and PK.

Six patients will initially be enrolled into the Phase 1b, dose-finding portion of Part 1 and will receive G1T28 200 mg/m^2 in combination with standard E/P therapy. Safety and available PK parameters from this initial cohort of 6 patients during Cycle 1 will be considered in making dose escalation/de-escalation decisions (if required).



a Assess the adjusted G1T28 dose in the next cohort of 6 patients based on DLTs and PK (if available) per the decision tree

b Maximum of 2 G1T28 dose reductions are allowed

- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of the Phase 1b, dose-finding portion of Part 1 and the available G1T28 PK parameters are as predicted, the dose-finding portion of Part 1 will end and subsequent patients will be enrolled into the Phase 2a expansion cohort of Part 1, utilizing a dose of G1T28 of 200 mg/m^2 in combination with E/P therapy.

- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of the Phase 1b dose-finding portion of Part 1, and the available G1T28 PK parameters suggest that the G1T28 dose needs to be escalated or de-escalated, a second cohort of 6 patients will be enrolled at the higher or lower predicted G1T28 dose in combination with E/P therapy.

- If there is > 1 DLT in the first cohort of 6 patients during Cycle 1 of the Phase 1b dose-finding portion of Part 1 and the available G1T28 PK parameters suggest that the G1T28 dose needs to be escalated or de-escalated (ie, in order to increase or decrease the magnitude and duration of G1 cell cycle arrest of HSPCs predicted by the PK/PD model and data from the Phase 1a Study G1T28-1-01; a second cohort of 6 patients will be enrolled at the modified G1T28 dose in combination with E/P therapy.

- If there is > 1 DLT in the first cohort of 6 patients enrolled in the Phase 1b dose-finding portion of Part 1 and the available G1T28 PK parameters from these 6 patients are as predicted, the dose of G1T28 should be decreased to 160 mg/m^2 and an additional 6 patients should be enrolled at the modified G1T28 dose in combination with E/P therapy.

- If there is > 1 DLT following a G1T28 dose of 160 mg/m^2 in combination with E/P therapy in the second cohort of patients and if available, PK parameters are as

predicted, an additional cohort of 6 patients will be enrolled at a further decreased G1T28 dose of 130 mg/m^2 in combination with E/P therapy.

- If there is > 1 DLT following the second dose reduction of G1T28 and if available, PK parameters from the third cohort are as predicted, 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 until the SMC can review the available data and make dose and cohort recommendations.

All dose-escalation/de-escalation decisions will be based on Cycle 1 safety data from all patients enrolled into the cohort and available PK data and will be reviewed by a safety monitoring committee (SMC) comprised of the sponsor, medical monitor, and the principal investigator(s) to determine the next dose level. If the G1T28 dose level for a subsequent cohort is adjusted by the SMC, the SMC may also recommend that all patients currently receiving G1T28 in combination with E/P therapy should have their G1T28 dose adjusted accordingly, starting with their next scheduled cycle. Additional cohorts for the Phase 1b dose-finding portion of Part 1 will be considered based on review of the safety data from all patients enrolled into the cohort and available PK data by the SMC. The dose for Part 2 will be obtained by utilizing all available safety and available PK data from patients enrolled in Part 1.

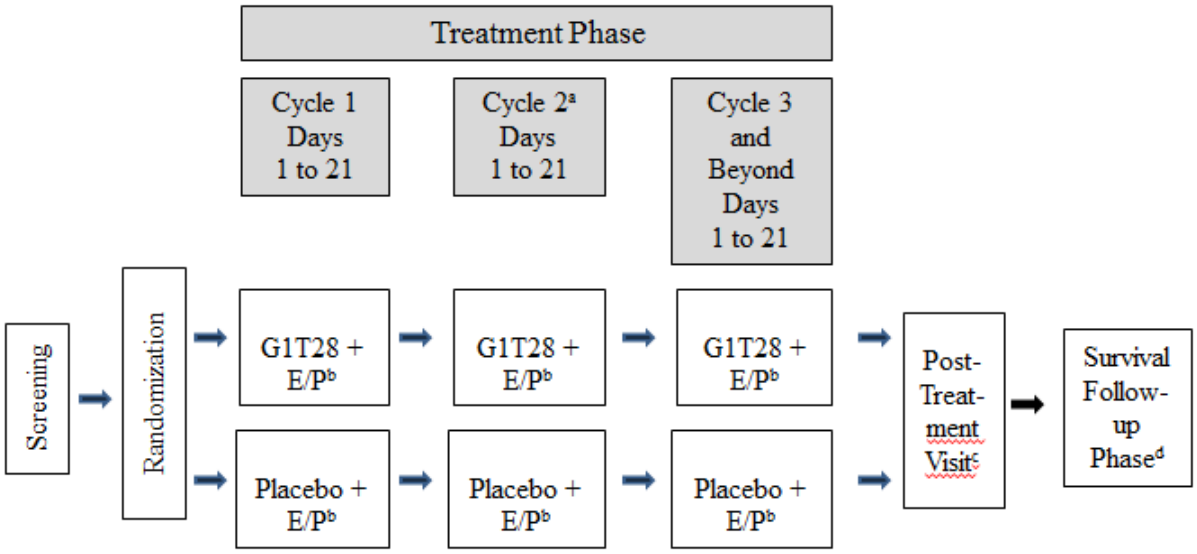
Part 1 Phase2a Expansion

Once the dose for Part 2 has been established, additional patients will be enrolled at the selected Part 2 dose in a Phase 2a expansion cohort in Part 1 until up to a total of 24 patients (6 from the Phase 1b dose-finding portion of Part 1 and up to 18 from the Phase 2a expansion cohort) have been enrolled at that dose. The Phase 2a expansion cohort in Part 1 will complete enrollment before enrollment into Part 2 commences.

Part 2

In Part 2, eligible patients will be randomized (1:1 fashion) to G1T28 or placebo administered IV once daily on Days 1 to 3 of E/P therapy (Figure 2). Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2). There will be no intrapatient dose modifications of G1T28 in Part 2 of the study.

Figure 2 Study Schema: Part 2



E/P = etoposide + carboplatin

a G1T28 + E/P will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). 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 G1T28 will be administered prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles

c Patients will return to the study center for a Post-Treatment Visit at 30 + 3 days after the last dose of study drug.

d The Survival Follow-up Phase will continue until at least 50% of the patients randomized to Part 2 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 2 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.

Criteria for Subsequent Cycles and Study Duration

In all parts of the study, study drug 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 (eg, after completing 6 cycles), 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 $\leq$ 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 Functional Assessment of Cancer Therapy –Lung (FACT-L) and Functional Assessment of Cancer Therapy – Anemia (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, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported outcome (PRO) scales; complete blood count (CBC) assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study.

The G1T28-02 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 29 months.

Part 1 is expected to be approximately 18 months, assuming 12 months of accrual, 2 weeks for screening, 4.5 months of treatment (assuming 6 cycles), and 1 month of safety follow-up.

Part 2 will begin after the Part 2 dose is identified from the Phase 1b dose-finding portion of Part 1 and the Phase 2a expansion portion of Part 1 has completed enrollment, which is expected to occur approximately 12 months after Part 1 begins. Part 2 is expected to be approximately 17 months, assuming 11 months of accrual, 2 weeks of screening, 4.5 months of treatment (assuming 6 cycles), and 1 month of safety follow-up.

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

Table 2 Schedule of Assessments

	Screening	Enroll	Cycle 1 and Every Odd Cycle[a] (21 days)						Cycle 2 and Every Even Cycle[a] (21 days)						Last Cycle	Post-Treatment Visit[b]	Survival Follow-up Calls[c]
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**8**	**10**	**15**	**1**	**2**	**3**	**8**	**10**	**15**	**22**		
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	X[g]			X		X		X	
Hematology	X		X[h]		X	X	X	X	X[h]		X	X	X	X	X	X	
Urinalysis	X		X[g]						X[g]							X	
ECG	X		X[i]		X[i]											X	
Pregnancy test[j]	X		X						X								
Randomization[k]		X															
Tumor Assessment[l]	X													X		X[l1]	
Tumor Testing[m]		X															
PK[n]			X		X												
G1T28 or Placebo[o]			X	X	X				X	X	X						
Carboplatin			X						X								
Etoposide			X	X	X				X	X	X						
FACT-L and FACT-An[p]			X				X		X				X			X	
Immunologic Marker			X													X	X
AEs[q]	X		X														
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 = pharmacokinetics

a G1T28 or placebo + E/P therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). 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.

c Monthly phone calls will be made to each patient that is in the long-term Survival Follow-up Phase. Patients will be followed for survival until at least 50% of the patients in Part 2 have died. Any anticancer therapies used will be collected. In addition, blood samples for hematology and immunologic marker assessment will be collected at 60 ± 7 days after the Post-Treatment Visit for patients in Part 2 only.

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, family history, documentation of tumor diagnosis, baseline signs and symptoms within 4 weeks prior to randomization, weight loss in the 6 months prior to randomization (≤ 5% or > 5%), and medications taken within 14 days of enrollment.

f Height will only be measured at the screening visit. Body surface area calculation (based on actual body weight) will be completed on Day 1 of each cycle and vital signs obtained immediately before and after G1T28 or placebo and E/P infusions. Vitals only need to be taken once between infusions.

g Clinical chemistry will be obtained (albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase [LDH], sodium, and blood urea nitrogen

[BUN]). Clinical chemistry and urine analysis may be obtained up to 72 hours prior to the first dose of each cycle of G1T28 or placebo + E/P therapy.

h Hematology will be obtained (hemoglobin, hematocrit, WBCs with differential, and platelet counts); Hematology may be obtained up to 24 hours prior to first dose of each cycle of G1T28/placebo + EP therapy.

i In Part 2 only, hematology will be collected at 60 days after the Post-Treatment Visit.

j Patients participating in the Phase 1b dose-finding portion of Part 1 of the study, who have PK samples obtained, will have ECGs completed at the following time points on Days 1 and 3 of Cycle 1: predose, end of infusion (EOI) of G1T28, 2 hours (± 10 minutes) after the start of G1T28, and 6.5 hours (± 15 minutes) after the start of G1T28. The 2-hour ECG will be completed once the etoposide infusion is complete.

k For female patients of childbearing potential, serum beta human chorionic gonadotropin (ß-hCG) at screening; serum or urine ß-hCG obtained up to 72 hours prior to Day 1 dose of G1T28 or placebo + E/P chemotherapy in each cycle.

l For patients enrolled in Part 2, randomization is to be done within 3 days prior to first dose of G1T28 or placebo + E/P chemotherapy, following confirmation that the patient is eligible for the study.

m For tumor assessment, all sites of disease should be assessed radiologically by computed tomography (CT) or magnetic resonance imaging (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 should 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 positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks). For those patients in the survival follow-up who have not progressed at the time of study drug 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.

m2: Brain scans with contrast (by CT or MRI) to be obtained with tumor assessment at screening (within 28 days of dosing) and at the Post-Treatment Visit

n 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 deoxyribonucleic acid (DNA), ribonucleic acid (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.

o Patients enrolled in Cohort 1 of the Phase 1b dose-finding portion of Part 1 will have G1T28, etoposide, and carboplatin PK samples collected on Days 1 and 3 (as applicable) of Cycle 1 at the time points specified in the protocol. Collection of PK blood samples from patients enrolled in additional cohorts of the Phase 1b dose-finding portion of Part 1 is optional.

p G1T28 or placebo will be administered as an IV infusion in 250 mL of D5W or sodium chloride solution 0.9% over 30 minutes prior to E/P chemotherapy on Days 1 to 3 of every cycle. If there is any volume remaining in the G1T28 or placebo infusion bag at the end of the 30 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 G1T28 or placebo on successive days should not be greater than 28 hours. The interval between the dose of G1T28 or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours. G1T28 or placebo will only be administered with E/P therapy. If administration of E/P therapy is discontinued, G1T28 or placebo should also be discontinued. Chemotherapy cannot be administered until after completion of the G1T28 or placebo infusion. If the second or third dose of G1T28 in any given cycle is not administered for any reason, do not administer the dose of etoposide or carboplatin chemotherapy on that day. After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported outcome (PRO) scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study.

q 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 G1T28 or placebo + E/P therapy. Patient-reported outcomes may be obtained up to 24 hours prior to the first dose of each cycle of G1T28 or placebo + E/P therapy.

r In Part 2 only, peripheral blood samples for immunologic marker assessment will be collected at predose on Day 1 of Cycles 1, 3, and 5; at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

s 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, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

2.3. Number of Patients

Overall, up to 110 patients will be enrolled in the study. The sample size for this study is determined by clinical rather than statistical considerations.

In Part 1, approximately 40 patients will be enrolled, assuming up to 3 cohorts. Cohorts will consist of 6 patients each in the Phase 1b dose-finding portion of Part 1 and up to 18 patients in the Phase 2a expansion portion of Part 1 at the selected dose to be used in Part 2. Additional patients may be enrolled in the Phase 1b dose-finding portion of Part 1 if more than 1 cohort is enrolled. In Part 2, 70 patients will be randomly assigned (1:1 ratio) to 1 of 2 groups: G1T28 administered IV with E/P therapy (Group 1) or placebo administered IV with E/P therapy (Group 2). With 35 patients, the precision for point estimates in each arm is as follows: the 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals are at most the observed proportion ± 0.157. The 95% CI width for continuous endpoints using the t-distribution are the observed mean ± 0.344*standard deviation of the endpoint.

The study will be conducted at up to 80 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 major deviations, will be reviewed and approved by G1 Therapeutics prior to the study unblinding.

3.1.1. Full Analysis Set

The full analysis set (FAS) includes all randomized patients who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib). Analyses using the FAS will be conducted on the basis of the assigned treatment. All efficacy analyses will be assessed using the FAS. The FAS will be used for analyses of tumor response, progression-free survival (PFS) and overall survival (OS).

3.1.2. Safety Analysis Set

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

3.1.3. Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set will include only those patients in FAS who have no major protocol deviations (as described in Section 3.2) and who received the treatment to which they were randomized or assigned. For patients who took the wrong treatment for part of the study, their data will be excluded from the PP analysis set. PP analysis set may be used to analyze selected endpoints to test the robustness of results. The criteria for inclusion in the PP subset will be finalized and documented prior to unblinding patients in Part 2 of the study.

3.1.4. Response Evaluable Analysis Set

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

3.2. Protocol Deviations

Certain protocol deviations are major in that they may affect the ability to assess the safety and efficacy of study drug. Patients with important deviations will be excluded from the PP analysis set. All patients who meet the definition of the FAS analysis set will be included in the FAS analysis set regardless of these deviations.

The criteria for inclusion in the PP set will be finalized and documented prior to unblinding patients in Part 2 of the study.

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 FAS, safety, and PP analysis sets but will be included in patients 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. A listing of patients whose blind was broken during the study (Part 2) will also be provided in the CSR, if appropriate; data from un-blinded patients will be included in the FAS and excluded from the PP population. Additional protocol deviations will be reviewed in a data review meeting to classify protocol deviations as minor or major, and to discuss the potential impact on statistical analysis.

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.

Based on the mechanism of action, it is also hypothesized that the effects of trilaciclib-induced myelopreservation may be more obvious after patients receive repeated rounds of chemotherapy. For example, SCLC patients treated with carboplatin and etoposide often have more dosing delays and hematologic-related adverse events (AEs) after multiple cycles due to repeated damage to the bone marrow. In contrast, addition of trilaciclib to carboplatin and etoposide is theorized to counteract the chemotherapy-induced damage and allow patients to receive multiple cycles of therapy with less dose delays and fewer hematologic-related AEs.

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.

Table 3 Prospectively Defined Analyses

Proportion of patients with febrile neutropenia during the treatment period
Duration of Grade 4 neutropenia
Duration of Grade 3/4 neutropenia
Average ANC over time (for all cycles; with and without GCSF subset analysis)
Average ANC NADIR over time (for all cycles; with and without GCSF subset analysis)
Average ANC at each scheduled Day 1 of a cycle (for all cycles; with and without GCSF subset analysis)
Average hemoglobin over time (for all cycles)
Average platelet count over time (for all cycles)
Average lymphocyte count over time (for all cycles)
Proportion of patients with RBC transfusions (includes actual or eligible) during the treatment period
Proportion of patients with platelet transfusions (includes actual or eligible) during the treatment period
Proportion of patients with GCSF use during the treatment period
Proportion of patients with ESA use during the treatment period
Proportion of patients with IV antibiotic use during the treatment period
Proportion of patients with infectious SAEs during the treatment period
Proportion of patients with pulmonary infectious SAEs during the treatment period
Time to first major adverse hematologic event (MAHE) which is defined to include components as the following: • hospitalization for a hematologic event (e.g. febrile neutropenia, thrombocytopenia, hemoptysis, etc.) • febrile neutropenia • death related to treatment (including backbone chemotherapy and trilaciclib) • dose delay/reduction due to ANC or platelet counts • duration of Grade 4 ANC > 5 days

- RBC transfusion (actual or eligible)
- platelet transfusion (actual or eligible)

ANC = absolute neutrophil count; ESA = erythropoiesis stimulating agent; GCSF = granulocyte-colony stimulating factor; IV = intravenous; NADIR = the lowest point; SAEs = serious AEs.

5. PRIMARY AND SECONDARY ENDPOINTS

The following general definitions will be applied to all endpoints derivation unless otherwise specified.

Term	Definition
Grade 4 neutropenia	ANC lab value that meets the common terminology criteria for adverse events (CTCAE) criteria for ≥ Grade 4 toxicity
Grade 3/4 neutropenia	ANC lab value that meets the CTCAE criteria for ≥ Grade 3 toxicity
Cycle baseline	The last non-missing value within the window starting from 3 days prior to the date/time of study drug 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 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 36.
Start of cycle	Day 1 of each cycle starts with the administration of study drug(s) (etoposide, carboplatin or trilaciclib)
Start of study	Day 1 of Cycle 1
Study baseline	The last non-missing value prior to, or on the date of administration of study drug(s) (etoposide, carboplatin or trilaciclib); 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 Prospectively-Defined Clinical Endpoints for Efficacy

5.1.1.1. Febrile Neutropenia AEs

A cycle is considered to have a febrile neutropenia AE if any date between the start and stop date of the AE overlaps with any date between the start of cycle and end of cycle. If an event ends on the cycle start day, it will not be counted as an event in that cycle unless the event also started on that day. For the treatment period, the total number of febrile neutropenia AE events is the number of cycles where at least one febrile neutropenia AE is observed. If a patient did not have any febrile neutropenia AE events, the value of 0 will be assigned to that patient. AEs during the study is captured in the electronic database. The event terms are coded using the Medical Dictionary for Regulatory Affairs (MedDRA Version 20.1) and “FEBRILE NEUTROPENIA” is

a preferred term which can be used to identify the proper AE records. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.1.

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

5.1.1.2. RBC Transfusions

Within a cycle, a RBC transfusion event is defined as either (1) an actual RBC transfusion, OR (2) eligible for RBC transfusion = hemoglobin < 8.0 g/dL. Therefore, for the treatment period, a total number of RBC transfusions (i.e. a RBC transfusion event = Yes) is obtained as the number of cycles in which there is at least one RBC transfusion event. If a patient did not have any RBC transfusion events, the value of 0 will be assigned to that patient. Hence, the total number of cycles without RBC transfusion is calculated as the total number of treatment cycles received – total number of cycles with RBC transfusion.

To define those cycles where a patient was eligible for a RBC transfusion, the lab value of hemoglobin (< 8.0 g/dL) must fall between start of cycle and end of cycle for that cycle. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

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

5.1.1.3. Platelet Transfusions

Similarly, within a cycle, a platelet transfusion event is defined as either (1) an actual platelet transfusion, OR (2) eligible for platelet transfusion = platelet count ≤ 10×10^9/L. Therefore, for the treatment period, a total number of platelet transfusions (i.e. a platelet transfusion event = Yes) is the number of cycles in which there is at least one platelet transfusion event. If a patient did not have any platelet transfusion events, the value of 0 will be assigned to that patient. Therefore, the total number of cycles without a platelet transfusion is calculated as the total number of treatment cycles received – total number of cycles with platelet transfusion.

To define those cycles where a patient was eligible for a platelet transfusion, the lab value of platelet count (≤ 10×10^9/L) must fall between start of cycle and end of cycle for that cycle. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

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

5.1.1.4. 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 administration 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 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.

5.1.1.5. **ESA Administrations**

Administration of erythropoiesis stimulating agents (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. If a patient did not receive an ESA, then the patient will be set to 0.

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 GCSF administration is the total number of cycles in which there is at least one ESAs 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 ESAs administration during the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with ESAs administration ≥ 1 is observed, No for other scenarios.

5.1.1.6. **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".

Those cycles where IV antibiotics are administered concurrently will be identified by comparing the start and stop dates of each antibiotic to the start of cycle and end of cycle. If any of the

dates of administration of any IV antibiotic overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having an IV antibiotic administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number IV antibiotics administration is the total number of cycles where IV antibiotics were administered. If a patient did not have any IV antibiotic use, the value of 0 will be assigned to that patient. The number of cycles where IV antibiotics were NOT given is calculated as total number of treatment cycles received – total number of cycles where IV antibiotics were administered.

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

5.1.1.7. Infection SAEs and Pulmonary Infection SAEs

Each infection SAE and 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 proper infection SAE and pulmonary infection SAEs records is as follows: if the system organ class (SOC) from MedDRA takes value "INFECTIONS AND INFESTATIONS", the preferred term (PT) takes values from Table 4, and the AE is a serious event.

Table 4 PT List for Grouping Infection AEs and Pulmonary Infection AEs

Category	Preferred terms	
Pulmonary Infection AEs	Bronchitis	
	Influenza	
	Pneumonia	
	Pneumonia bacterial	
	Respiratory tract infection	
	Upper respiratory tract infection	
	Viral upper respiratory tract infection	
Infection AEs	Anal abscess	Oral herpes
	Bacteraemia	Pharyngitis streptococcal
	Bronchitis	Pneumonia
	Candida infection	Pneumonia bacterial
	Chronic sinusitis	Respiratory tract infection
	Conjunctivitis	Sepsis
	Infection	Skin infection
	Influenza	Upper respiratory tract infection
	Nasopharyngitis	Urinary tract infection
	Oral candidiasis	Urosepsis
		Viral upper respiratory tract infection

A cycle is considered to have an infection SAE if any date between the start and stop date of the AE overlaps with any date between the start of cycle and end of cycle. If an event ends on the

cycle start day, it will not be counted as an event in that cycle unless the event also started on that day. For the treatment period, the total number of infection SAE events is the number of cycles where at least one infection SAE is observed. If a patient did not have any infection SAE events, the value of 0 will be assigned to that patient. 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 SAE events ≥ 1 is observed, No for other scenarios.

Similarly, a cycle is considered to have a pulmonary infection SAE if any date between the start and stop date of the AE overlaps with any date between the start of cycle and end of cycle. If an event ends on the cycle start day, it will not be counted as an event in that cycle unless the event also started on that day. For the treatment period, the total number of pulmonary infection SAE events is the number of cycles where at least one pulmonary infection SAE is observed. If a patient did not have any pulmonary infection SAE events, the value of 0 will be assigned to that patient. 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 SAE events ≥ 1 is observed, No for other scenarios.

5.1.1.8. Duration of Grade 4 Neutropenia

Grade 4 neutropenia is defined as the lab value of ANC ≥ Grade 4 event CTCAE toxicity grade criteria (i.e. ANC value is $< 0.5 \times 10^9$/L). For the treatment period, the total number of Grade 4 neutropenia 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 ANC ≥ Grade 4 events, the value of 0 will be assigned to that patient. Unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

Within each cycle, the duration (days) of each reported Grade 4 neutropenia event 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:

(i) For a cycle where the Grade 4 neutropenia event does not resolve by end of the cycle, the duration will be assigned as above except the end date will be the end of cycle.

(ii) For a cycle where the patient dies, withdraws consent, or is lost to follow-up during the Grade 4 neutropenia event, the duration will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of cycle.

For the treatment period, the overall duration (days) of Grade 4 neutropenia events is the median value among the duration (days) of Grade 4 neutropenia events 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 KM 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.

5.1.1.9. **Duration of Grade 3/4 Neutropenia**

Grade 3/4 neutropenia is defined as the lab value of ANC ≥ Grade 3/4 event per CTCAE toxicity grade criteria (i.e. ANC value is < 1.0 x 10^9/L). For the treatment period, the total number of Grade 3/4 neutropenia events is the number of cycles where at least one ANC value is < 1.0 x 10^9/L. For example, if Cycle 2 has two ANC values that are both < 1.0 x 10^9/L, this only counts as one event. If a patient did not have any ANC ≥ Grade 3/4 events, the value of 0 will be assigned to that patient. Unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

Within each cycle, the duration (days) of each reported Grade 3/4 neutropenia event is defined as the number of days from the date of first ANC value of <1.0 x 10^9/L observed between start of cycle and end of cycle, to the date of first ANC value ≥ 1.0 x 10^9/L that meets the following criteria: (1) occurs after the ANC value of <1.0 x 10^9/L and (2) no other ANC values <1.0 x 10^9/L occur between this day and end of cycle. The following censoring rules will be applied in the calculation:

(i) For a cycle where the Grade 3/4 neutropenia event does not resolve by end of the cycle, the duration will be assigned as above except the end date will be the end of cycle.

(ii) For a cycle where the patient dies, withdraws consent, or is lost to follow-up during the Grade 3/4 neutropenia event, the duration will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of cycle.

For the treatment period, the overall duration (days) of Grade 3/4 neutropenia events is the median value among the duration (days) of Grade 3/4 neutropenia events 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 KM 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.

5.1.1.10. ANC, Platelet Count, Absolute Lymphocytes, and Hemoglobin Change over Time

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

Also, for the ANC, the observed lab value at each scheduled Day 1 of a cycle will be properly flagged for further analysis. The scheduled Day 1 of cycle will follow the scheme defined in the protocol regardless of the potential cycle delay, for example, if Cycle 2 is delayed 7 days from Cycle 1 due to ANC recovery, Day 22 from the first dose date of study drug in Cycle 1 will the scheduled Day 1 of Cycle 2.

5.1.1.11. Time to First Major Adverse Hematologic Event (MAHE)

As a composite measure of trilaciclib effect, MAHE is based on a combination of individual components specified in Table 5, which also include details about the derivation or data source for each component. Time to first occurrence of a MAHE event is defined as the first time to observe an interested event among all the component, starting from the first dose date of study drug administration.

Therefore, for a patient with presence of MAHE events, time (months) to first occurrence of a MAHE event will be the minimum among the 7 potentially derived duration (i.e. calculated as (date of first occurrence of a MAHE component event – first dose date of study drug administration + 1)/30).

Table 5 Component of MAHE and the Suggested Data Source/Derivation Algorithm

Seq #	Component of MAHE	Criteria to identify the date of first occurrence of event
1	Hospitalization for a hematologic event (e.g. febrile neutropenia, thrombocytopenia, hemoptysis, etc)	Each hospitalization for a hematologic event (e.g. febrile neutropenia, thrombocytopenia, hemoptysis, etc.) is captured in AE data of electronic database. The event terms are coded using the MedDRA Version 20.1. Some suggested PTs are listed in Table 6. These PTs will be broken into those that are always counted if they result in hospitalization, and those that will be subject to a case by case medical review to determine if the hospitalization is a hematologic event. All review will be finalized prior to study unblinding.
2	Febrile neutropenia	Detailed in Section 5.1.1.1
3	Death related to treatment (including backbone chemotherapy and trilaciclib)	An AE with its outcome being death, if its relationship to any of the study drugs (etoposide, carboplatin, or trilaciclib) is “Possibly Related”, “Probably Related”, or “Definitely Related”.
4	Dose delay/reduction due to ANC or platelet counts	Detailed in Section 5.1.3.4
5	Duration of Grade 4 neutropenia > 5 days	Detailed in Section 5.1.1.8. If the duration (days) within a cycle is censored, even the duration of Grade 4 neutropenia

Seq #	Component of MAHE	Criteria to identify the date of first occurrence of event
		is ≤ 5 days, the event will still be considered to meet the criteria. 5.1.1.2
6	RBC transfusion (actual or eligible)	Detailed in Section 5.1.1.2
7	Platelet transfusion (actual or eligible)	Detailed in Section 5.1.1.3

A patient with absence of any MAHE events will be censored at the date of the last assessment/contact date prior to or on the day of study completion/discontinuation, or lost to follow-up, whichever is earlier.

Table 6 PT list for Meeting the Criteria of Hospitalization for a Hematologic Event

PTs always included	PTs to be reviewed for possible inclusion
FEBRILE NEUTROPENIA	RESPIRATORY FAILURE
NEUTROPENIA	PNEUMONIA
ANAEMIA	HAEMOPTYSIS
THROMBOCYTOPENIA	
NEUTROPHIL COUNT DECREASED	
HEMOGLOBIN DECREASED	
ANAEMIA MACROCYTIC	
RED BLOOD CELL COUNT DECREASED	
PLATELET COUNT DECREASED	

5.1.2. Exploratory Efficacy Endpoints

5.1.2.1 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.

5.1.2.2 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.

5.1.2.3 FACT-L and FACT-An

The FACT-L is a 36-item self-report instrument that measures multidimensional quality of life (QoL) by asking patients to rate a series of statements. FACT-L consists of the 27-item FACT—general (FACT-G) combined with the 9-item lung cancer-specific subscale (2 of the 9 items are not scored, that is, B5 = "I am bothered by hair loss" and L5 = "I regret my smoking").

The FACT-G contains four generic cancer-specific subscales including the 7-item physical well-being (PWB), 7-item social/family well-being (SWB), 6-item emotional well-being (EWB), and 7-item functional well-being (FWB) subscales. The 7-item Lung Cancer Subscale (LCS) assesses the impact of symptoms commonly reported by lung cancer patients, including shortness of breath, loss of weight, and chest tightness. The 20-item anemia subscale consists of the 13-item fatigue component and 7 items for non-fatigue; hence, fatigue and other symptoms of anemia (e.g., dizziness, joint aches, etc) are measured using an anemia-specific symptom scale that assesses self-report of the cognitive, physical, and emotional manifestations of anemia. All the questions are rated on a five-point Likert-type scale ranging from 0 (not at all) to 4 (very much).

Table 7 List of Items Which Need Subtraction before Subscale or Total Score Calculation

Subscale	Item ID	Items description	Value to be used for score calculation
PWB	All 7 items		4 - observed value
EWB	GE1	I feel sad	4 - observed value
	GE3	I am losing hope in the fight against my illness	4 - observed value
	GE4	I feel nervous	4 - observed value
	GE5	I worry about dying	4 - observed value
	GE6	I worry that my condition will get worse	4 - observed value
LCS	B1	I have been short of breath	4 - observed value
	C2	I am losing weight	4 - observed value
	L2	I have been coughing	4 - observed value
	L3	I feel tightness in my chest	4 - observed value
Anemia	HI7	I feel fatigued	4 - observed value
	HI12	I feel weak all over	4 - observed value
	An1	I feel listless ("washed out")	4 - observed value
	An2	I feel tired	4 - observed value
	An3	I have trouble starting things because I am tired	4 - observed value
	An4	I have trouble finishing things because I am tired	4 - observed value

Subscale	Item ID	Items description	Value to be used for score calculation
	An6	I have trouble walking	4 - observed value
	An8	I need to sleep during the day	4 - observed value
	An9	I feel lightheaded (dizzy)	4 - observed value
	An10	I get headaches	4 - observed value
	B1	I have been short of breath	4 - observed value
	An11	I have pain in my chest	4 - observed value
	An12	I am too tired to eat	4 - observed value
	An14	I need help doing my usual activities	4 - observed value
	An15	I am frustrated by being too tired to do the things I want to do	4 - observed value
	An16	I have to limit my social activity because I am tired	4 - observed value

Calculation of the FACT scores and methods to deal with missing data will be handled according to the standard scoring guidelines. Based on the FACT scoring guide, Table 7 identifies those items that must be subtracting the response from "4". After the subtraction in proper items, the subscale score or relevant total score can be calculated. When there are missing data, a subscale with at least 50% answered items enables valid subscale score calculation (e.g., a minimum of 4 answered items from 7 items, 4 answered items of 6 items).

The total score is then calculated as the sum of the un-weighted subscale scores. However, two rules are defined as follows for a valid total score when there are missing data

- ALL of the component subscales have valid scores;
- at least 80% answered items in overall (e.g. e.g., at least 22 of 27 FACT-G items completed);

The detailed algorithms to calculate the subscale or relevant total score are defined in Table 8. For both subscale and total score, higher scores represent better functioning and better QoL.

Table 8 Algorithm for Subscale Score and Total Score

Scale (no. of items)	Algorithm of score calculation
FACT-G (27)	
PWB subscale (7)	It is calculated as 7 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 4 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 28.
SWB subscale (7)	It is calculated as 7 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 4 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 28.
EWB subscale (6)	It is calculated as 6 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 4 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 24.
FWB subscale (7)	It is calculated as 7 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 4 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 28.
Total FACT-G score (27)	Sum of subscale scores from PWB, SWB, EWB, and FWB, then it is calculated as 27 × [Sum of subscale scores] ÷ [N of items answered], however, – if any of the subscale score is missing, the total score is set to missing; or

Scale (no. of items)	Algorithm of score calculation
	– if there are ≥ 6 missing items scores, the total score is set to missing; total FACT-G score ranges from 0 to 108.
LCS subscale (7)	
Total LCS subscale (7)	It is calculated as 7 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 4 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 28.
Total FACT-L (FACT-G + LCS subscale; 34)	Sum of subscale scores from PWB, FWB, EWB, FWB, and LCS, then it is calculated as 34 × [Sum of subscale scores] ÷ [N of items answered], however, – if any of the subscale score is missing, the total score is set to missing; or – if there are ≥ 7 missing items scores, the total score is set to missing; total FACT-L score ranges from 0 to 136.
Trial Outcome Index (TOI) (21)	Sum of subscale scores from PWB, SWB, and LCS, then it is calculated as 21 × [Sum of subscale scores] ÷ [N of items answered], however, – if any of the subscale score is missing, the total score is set to missing; or – if there are ≥ 5 missing items scores, the total score is set to missing; TOI ranges from 0 to 84.
Anemia subscale (20)	
Fatigue subscale (13)	It is calculated as 13 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 6 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 52.
Non-fatigue subscale (7)	It is calculated as 7 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 4 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 28.
Total anemia subscale (20)	It is calculated as 20 × [Sum of item scores] ÷ [N of items answered]. If there are ≥ 11 missing items scores, the subscale score is set to missing. The subscale score ranges from 0 to 80.
Total FACT-An (FACT-G + anemia subscale; 47)	Sum of subscale scores from PWB, FWB, EWB, FWB, and anemia, then it is calculated as 47 × [Sum of subscale scores] ÷ [N of items answered], however, – if any of the subscale score is missing, the total score is set to missing; or – if there are ≥ 10 missing items scores, the total score is set to missing; total FACT-L score ranges from 0 to 188.
Anemia TOI (34)	Sum of subscale scores from PWB, SWB, and anemia, then it is calculated as 34 × [Sum of subscale scores] ÷ [N of items answered], however, – if any of the subscale score is missing, the total score is set to missing; or – if there are ≥ 7 missing items scores, the total score is set to missing; anemia TOI ranges from 0 to 136.

The extreme (best and worst) on study values and minimum and maximum change for each FACT subscale and total score will be derived.

Clinically meaningful improvement in LCS is a binary variable (Yes or No) — Yes if the LCS subscale score is ≥7% increase from baseline, or ≥ 2 change from baseline, No for other non-missing scenarios. Similarly, clinically meaningful deterioration is a binary variable (Yes or No) — Yes if the LCS subscale score is ≥7% reduction from baseline, or ≤ -2 change from baseline, No for other non-missing scenarios.

5.1.2.4 Neutrophil-lymphocyte Ratio (NLR) and Platelet-lymphocyte Ratio (PLR)

NLR will be derived using the ANC and absolute lymphocyte count (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. objective response rate (ORR), PFS, and etc.].

5.1.3. Chemotherapy Exposure And Compliance Endpoints

5.1.3.1 Duration of Exposure

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

5.1.3.2 Number of Cycles Received

Patients are considered to have started a cycle if they have received at least one dose of any study drug (etoposide, carboplatin, and trilaciclib). In addition to the numeric summary for the number of cycles, the number of cycles will be categorized as 1, 2, 3, 4, 5, and ≥ 6.

5.1.3.3 Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 9.

Table 9 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Trilaciclib [§]	Etoposide	Carboplatin
Dosing schedule per protocol	200 mg/m^2 IV on Days 1 to 3 of a 3-week cycle	100 mg/m^2 IV on Days 1 to 3 of a 3-week cycle	5 AUC on Day 1 of a 3-week 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)].	Total dose administered (Prescribed AUC and actual dose in mg)
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)]	Sum of the doses administered to a patient in the duration of exposure (in total prescribed AUC and total dose in mg)
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)]	Cumulative Dose (total prescribed AUC) / (duration of exposure / 7) [AUC/ week]
Relative dose intensity (%)	100 * [Dose intensity (mg/m^2/week) / (600 /3 (mg/m^2/week)]	100 * [Dose intensity (mg/m^2/week) / (300 /3 (mg/m^2/week)]	100 * [Dose intensity (AUC/week) / (5/3) (AUC/week)]

Parameter	Trilaciclib [§]	Etoposide	Carboplatin
Relative Dose (%)	100 * [Cumulative dose (mg/m^2) / (600 × number of cycles (mg/m^2)]	100 * [Cumulative dose (mg/m^2) / (300 × number of cycles (mg/m^2)]	100 * [Cumulative dose (AUC) / (5 × number of cycles (AUC)]

[§] Two different doses (200mg/m^2 and 240mg/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.
AUC = area under curve; BSA = body surface area; IV = intravenous.

5.1.3.4 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 electronic case report form (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. The reasons for missed doses will be summarized in the following categories: (1) Adverse Event, (2) Logistical/Administrative Issues, and (3) Other.
- Dose (mg/m^2) reductions are not permitted for trilaciclib. Dose reductions for carboplatin and etoposide 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.
- Dose interruptions for all drugs are also captured on the dosing page and will be summarized for each study drug.

5.2. Safety Endpoints

5.2.1. Adverse Events (AEs)

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 including the post-treatment visit. AEs are graded by investigator according to CTCAE, Version 4.03.

Any AE that started on or after the first dose of study drugs 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 discontinuation or study withdrawal, AEs leading to death, 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, the date of first dose of study drug 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, the date of the first dose of study drug 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 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, 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 the date of the first dose of study drug 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 10 outlines those terms that will be consolidated.

Table 10 Preferred Terms to Be Consolidated

Presented term in the table	Preferred Term
Neutropenia	Neutropenia
	Febrile neutropenia
	Neutrophil count decreased
Anaemia	Anaemia
	Anaemia macrocytic
	Red blood cell count decreased
	Hemoglobin decreased
Thrombocytopenia	Thrombocytopenia
	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 that have a start date on the same

date study drug is administered will be summarized and presented in order of decreasing frequency: angioedema, back pain, bronchospasm, wheezing, chest pain, non-cardiac chest pain, hyperhidrosis, malignant dysphagia, dysphagia, oedema, swelling face, flushing, dysphonia, hypotension, hypoxia, paraesthesia oral, pain, phlebitis, pruritic, pyrexia, rash, dermatitis allergic, drug eruption, infusion site rash, injection site rash, rash pruritic, erythema, infusion site erythema, injection site erythema, chills, dyspnoea, syncope, tachycardia, throat tightness, injection site ulcer and mucocutaneous ulceration.

5.2.2. 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, BSA will be computed using DuBois-DuBois formula as 0.20247 × [height (m)]$^{0.725}$ × [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 11:

Table 11 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

5.2.3. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 12 will be measured.

Table 12 Laboratory Assessment

Lab Category	Lab tests
Hematology	hemoglobin, hematocrit, white blood cell (WBC) with differential, platelet counts, ANC, ALC, Monocyte Absolute, Basophil Absolute, Eosinophil Absolute, and other non-protocol specified tests
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),

Lab Category	Lab tests
	sodium, and Blood Urea Nitrogen (BUN), and other non-protocol specified tests
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 non-protocol specified tests and urinalysis 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 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

5.2.4. 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 13. ECG results are interpreted as normal, abnormal but not clinically significant, or abnormal and clinically significant.

Table 13 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

ECG Parameter	Criterion value
QTcB, QTcF Intervals	≥ 500ms
	≥ 480ms
	≥ 450ms
	≤ 300ms
	Change from baseline ≥ 30 ms
	Change from baseline ≥ 60 ms

5.2.5. 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.

5.2.6. Tumor Responses and Clinical Benefit

For tumor assessment, all sites of disease will be assessed radiologically by CT or MRI at screening, every other cycle while on treatment and every 2 months in survival followup, until the date of (i) disease progression as defined by RECIST 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 three ways: (1) derived programmatically using the information from target lesions (TL), non-target lesions (NTLs) and new lesions as entered into the eCRF, (2) by the investigator and collected in the eCRF and (3) by Blinded Independent Central Review (BICR) which is described in the Independent Review Charter.

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).

5.2.6.1. 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 computed tomography (CT) or magnetic resonance imaging (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 14 gives definition of TL visit responses.

Table 14 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 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 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.

5.2.6.2. 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 15:

Table 15 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.

5.2.6.3. Time Point Response (TPR)

Table 16 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 16 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 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 5.2.6.1 and 5.2.6.2.

For a scheduled tumor scan 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

5.2.6.4. Best Overall Response (BOR)

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 1.1 (Eisenhauer et al, 2009) or by clinical criteria (this will not apply to the BICR analysis); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

A patient's BOR will be determined based on Table 17. For data-driven scenarios which may not be covered by Table 17, 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 17 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 v1.1. 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 of CR or PR and the first date that progressive disease is documented by RECIST (or clinical progression for investigator or derived analyses, whichever comes first) 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 PFS in Section 5.2.7.

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, BICR responses, and investigator responses.

ORR, $ORR_{UNCONFIRMED}$, DOR and CBR will be summarized for Part 1, Part 2, and Part 1 + Part 2 patients treated with 240mg/m^2.

5.2.7. 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, progression-free survival (PFS) is defined as the time (months) from date of first dose date of study drug 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 1.1 (Eisenhauer et al,

2009) or by clinical criteria (this will not apply to the BICR analysis); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

PFS will be calculated using two response data sets: derived and BICR. For PFS determined by BICR, only progression per RECIST will be considered. For PFS as determined by derived, either clinical progression or progression by RECIST (whichever comes first) 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 18.

Table 18 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 for patients in Part 1 or date of randomization for patients in Part 2	Censored
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	Date of the first reported progression	Progressed
Death without a PD	Date of death	Progressed
Investigator claim of clinical progression	Date of the investigator assigned PD	Progressed

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.

5.2.8. Overall Survival

Overall survival is calculated as the time (months) from date of first dose of study drug 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 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 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.

6. ANALYSIS METHODS

6.1. General Principles of Analysis

6.1.1. General Methodology

In general, all efficacy, safety and PK variables will be summarised using descriptive statistics and graphs as appropriate. Continuous variables will be summarised by descriptive statistics (sample size (n), mean, standard deviation (SD), minimum, median, and maximum). Categorical variables will be summarised in frequency tables (frequencies and percentages). For PK variables, the geometric mean and coefficient of variation (CV) will be used instead of the arithmetic mean and SD, if appropriate. Time to event variables will be analysed 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® 9.1 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonisation (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. In addition, the programming needed to generate a subset of outputs will be validated by an independent validation vendor. 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 19.

Table 19 Treatment Display in TLFs

Study Part	G1T28 Dose	Treatment Description in Data Display
Part 1	200 mg/m^2	G1T28 200 mg/m^2
Part 1	240 mg/m^2	G1T28 240 mg/m^2
Part 1		G1T28 Total [a]
Part 2	240 mg/m^2	G1T28 240 mg/m^2
Part 2	Placebo	Placebo
Parts 1 and 2	240 mg/m^2	G1T28 240 mg/m^2 [b]

[a] Summarize all G1T28 dose groups in Part 1.
[b] Summarize all G1T28 dose group 240 mg/m^2 in Part 1 and Part 2, it will be included in the summary for safety data.

All statistical tests will be conducted at a two-sided significance level of 20% unless otherwise specified. For Part 2 data, the G1T28 + E/P therapy will be compared to the placebo + E/P therapy 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 SD and standard error (SE). The derived variables will be presented with 1 decimal place. Percentages will be reported with 1 decimal point; 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.

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 within each cycle – defined as Day 1 – to the dates that the scheduled visits occurs. 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 20. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patients 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 + 36 to last assessment date prior to the start of survival follow-up". For the survival follow-up visit, it will only be applicable for the hematologic parameters.

Table 20 Visit Windowing

	Cycle 1/ Odd cycle (2X-1)						Cycle 2/ Even cycle (2X)						Post-treatment	Survival follow-up [e]
Visit	**C1D1**	**C1D3**	**C1D8**	**C1D10**	**C1D15**	**EOC1**	**C2D1**	**C2D3**	**C2D8**	**C2D10**	**C2D15**	**EOC2**		
Scheduled Day [a]	1	3[f]	8[f]	10[f]	15	22	1	3[f]	8[f]	10[f]	15	22		
ECOG	Day 1						Day 1						First dose date of last cycle + 36 to last assessment date prior to the start of survival follow-up	Relative to the date of post-treatment, the last assessment falling in the window between 1 and 67.
Clinical Chemistry [b]	Day -3 - 1		1-11		12-EOC		Day -3 - 1		1-11		12-EOC			
Hematology [c]	Day -3 - 1	1 to 5	6 to 9	10 to 12	13 to 18	19 to EOC	Day -1 - 1	1 to 5	6 to 9	10 to 12	13 to 18	19 to EOC		
Urinalysis [b]	Day -3 - 1						Day -3 - 1							
FACT-L and FACT-An [d]	Day -1 - 1			1 to EOC			Day -1 - 1			1 to EOC				

[a] The scheduled day is relative to the Day 1 of each cycle.
[b] Hematology, clinical chemistry and urine analysis may be obtained up to 72 hours prior to the first dose of each cycle of G1T28 or placebo + E/P therapy.
[c] Hematology may be obtained up to 3 days prior to first dose of G1T28/placebo + EP therapy in Cycle 1, and 1 day prior to first dose for subsequent cycles.
[d] 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 G1T28 or placebo + E/P therapy. Patient-reported outcomes may be obtained up to 24 hours prior to the first dose of each cycle of G1T28 or placebo + E/P therapy.
[e] 60 ± 7 days after the post-treatment visit only for hematologic parameters and immunologic biomarker. The data is collected only for patients in Part 2.
[f] If Day 1 is included in the windowing, the associated assessment must be post G1T28 infusion.
Note: The end date of a cycle (EOC) is defined as the date of Day 1 study drug administration of its next cycle. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 36 relative to the first dose of the cycle. Hence, for the last cycle, the window for EOC is 19-36.

6.1.4. Adjustment for Covariates

The baseline ECOG status (0, 1, and 2) which was used as the stratification factor will be included as a covariate in relevant statistical modeling for data from Part 2.

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 (Part 1 only)
- Number of patients randomized (Part 2 only)
- Number of patients randomized and not dosed (Part 2 only)
- Number of patients dosed and not randomized (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 (discontinued study drug or continue on study drug)
- Number and percentage of patients in the FAS who discontinued study drug
- Number and percentage of patients in the FAS who discontinued study drug before 6 cycles
- Number and percentage of patients in the FAS who discontinued study drug after 6 cycles
- Reason for study drug discontinuation
- End of study status (discontinued study or continue in the survival follow-up)
- Number and percentage of patients in the FAS 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, height, body weight, ECOG status (0, 1, and 2), smoking history (never smoker, former smoker and current smoker, smokeless tobacco, etc), and BMI will be summarized and listed.

6.2.3. Disease Characteristics and Prior Therapies

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 age at initial diagnosis of lung cancer will be listed only.

The prior anti-cancer therapies, such as prior systemic anti-cancer therapy (Yes or No), prior anti-cancer surgery (Yes or No, and if Yes, related to lung cancer), and prior radiotherapy (Yes or No), will be summarized and listed.

6.2.4. Medical History

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

The number and percentage of randomized patients 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.

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. Concomitant medications are defined as those taken by the patient at any time between the date of study drug 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, the date of first dose of study drug 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, the date of the first dose of study drug 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 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 month will be used to complete the end date of the medication;
- If the day and month parts of 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, 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 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

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 and subsequent anti-cancer therapy will be summarized separately 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. The data will be presented in a patient listing.

For subsequent anti-cancer therapy, if the term contains the word "RADIATION", the therapy will be classified to radiotherapy; it is classified as systemic anti-cancer therapy unless the therapy can be grouped to surgery. The number and percentage of randomized patients receiving subsequent anti-cancer therapy will be provided by systemic anti-cancer therapy (by drug name and by line), radiotherapy, and surgery. All subsequent anti-cancer therapies 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 vs placebo), if applicable, will be performed only for those prospectively-defined endpoints outlined in Section 5.1.1. For these comparisons, all statistical tests will be conducted at a two-sided significance level of 20% 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. Graphical presentation of efficacy results will be appropriately performed as needed.

6.2.7.1. Prospectively-Defined Efficacy Analyses

Detailed information for the prospectively-defined efficacy endpoints can be found in Section 5.1.1. A binary response variable (Yes, No) will be analyzed to compare G1T28 and placebo using stratum-adjusted method to account for the ECOG status (0-1 vs 2) as the stratification factor. 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 Cochran-Mantel-Haenszel (CMH) method. The following binary response variables will be analyzed:

- Occurrence of a febrile neutropenia AE during the treatment period (refer to Section 5.1.1.1);
- Occurrence of a RBC transfusion (actual and eligible) during the treatment period (refer to Section 5.1.1.2);
- Occurrence of a platelet transfusion (actual and eligible) during the treatment period (refer to Section 5.1.1.3);
- Occurrence of a GCSF administration during the treatment period (refer to Section 5.1.1.4);

- Occurrence of an ESA administration during the treatment period (refer to Section 5.1.1.5);
- Occurrence of an IV antibiotic administration during the treatment period (refer to Section 5.1.1.6);
- Occurrence of an infection SAE during the treatment period (refer to Section 5.1.1.7);
- Occurrence of a pulmonary infection SAE during the treatment period (refer to Section 5.1.1.7).

Time (days) to event endpoints 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 for endpoints described in Sections 5.1.1.8, 5.1.1.9, and 5.1.1.11.

In addition to the summary from Kaplan-Meier method, for the endpoints of

- Overall duration (days) of Grade 4 neutropenia;
- Overall duration (days) of Grade 3/4 neutropenia;
- Time (days) to first occurrence of a MAHE event,

the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the ECOG status (0-1 vs 2) as the stratification factor. 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 baseline ECOG status (0-1 vs 2) will be included as fixed effects. For the time (days) to first occurrence of a MAHE event, a graphical display of cumulative incidence will be presented.

For the endpoints specified in Section 5.1.1.10, in addition to descriptive statistics summary, appropriate graphical display will be provided to help viewing the trend of change over time. Moreover, each of the ANC change over time (i.e. observed value at windowed visit, cycle NADIR, and ANC at each scheduled Day 1 of a cycle) 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.

6.2.7.2. Exploratory Efficacy Analyses

For all these exploratory endpoints listed in Sections 5.1.2.1, 5.1.2.2, 5.1.2.3, and 5.1.2.4, 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.

6.2.7.3. Exposure Endpoints

The extent of drug exposure and dose modifications is considered as important efficacy endpoints for trilaciclib. The study dosing records and the derived dosing endpoints will be listed.

Duration on treatment and number of cycles will be summarized by treatment. For each study drug, the dosing endpoints described in Section 5.1.3 will be summarized by treatment.

Dose modification will be summarized for each study drug (trilaciclib, etoposide and carboplatin) including 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 its reason;
- Number of patients with dose interruption and its reason.

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 number of patients discontinuing study drug will also be summarized along with the reason for discontinuation.

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. Adverse Events

Number and incidences 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 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 study drug (trilaciclib, carboplatin, and etoposide), and the drug related AE summary will be appropriately evaluated by 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, and AEs leading to study drug discontinuation or study withdrawal will be provided.

For the AEs related to infusion and related to hematologic toxicity, the criteria for identifying them 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.

6.2.8.2. 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, its normal reference ranges, and its CTCAE grade (when possible) will be provided.

6.2.8.3. Vital Signs

For vital sign parameters Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature, 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 11) during the treatment period will be presented. A listing of all vital sign data will be provided.

6.2.8.4. 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.

6.2.8.5. Physical Examination

A listing of physical examination findings for all patients will be provided.

6.2.8.6. 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 of potentially clinically significant findings are defined in Table 13. 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.

6.2.8.7. Analyses of Objective Response

The number and percentage of patients in each category of TPR according to the investigator tumor assessment (CR, PR, SD, PD, or NE) will be presented. Also, the number and percentage of patients in each category of derived 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 5.2.6.

Similar analyses will be repeated based on the derived responses according to the RECIST 1.1, and based on the data from BICR. A cross tabulation of BICR BOR versus the derived BOR will be presented, by treatment group.

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.

DOR (investigator, derived, and BICR) will be summarized using the Kaplan-Meier method, displayed graphically when appropriate, and summarized with median, 25% and 75% percentiles, and their 95% CIs.

The binary endpoint (Yes, No) of ORR for the two treatments (trilaciclib and placebo) in Part 2 will be analyzed to compare trilaciclib and placebo using stratum-adjusted method to account for the ECOG status (0-1 vs 2) as the stratification factor. 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 population and FAS population. The supportive data listings will also be provided.

6.2.8.8. Analyses of PFS and OS

The analysis method as described in Section 6.2.7.1 for time to event data will be applied to the following variables

- PFS (BICR and derived)
- OS

The analyses are based on the FAS. The supportive data listings will also be provided.

For the PFS from both BICR and derived responses and OS, a comparison will be conducted between G1T28 and placebo in Part 2. The two-sided p-value from a Cox proportional hazard model will be presented, the model includes treatment and baseline ECOG status (0-1 vs 2) as fixed effects. The hazard ratio (HR) between the two treatment groups, together with its 95% CIs will be presented.

6.2.9. Subgroup Analyses

The PFS, OS, ORR may be examined in the following subgroups:

- Age group (ages 18 to 65; 65-75; >75).
- Gender (Male; Female).
- ECOG performance status (0-1; 2).
- Race (Caucasian; non-Caucasian).
- 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 Ki68, RB, and CCND1.
2. SCLC tumor samples may be assessed for markers to 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 analysis will occur after the last patient has completed the Post-Treatment Visit. All study data collected up through the time of the final analysis data cut-off, including Follow-Up Survival Phase results, will be summarized in the final analysis. Unblinding will occur at the time of the final analysis.

The end of study analysis for the CSR will be conducted when the OS data of Part 2 are approximately 70% mature (approximately 55 death events). Reported results will include the subset of data not previously reported during the final analysis.

7. CHANGE FROM THE PROTOCOL

The endpoints and analyses listed below are based on the Statistics Section in the Protocol Amendment 7, dated 11 May 2016. The list displays the endpoints and analyses which are removed from the initial analysis and are therefore not described in the SAP..

Protocol Section 13.3.1 (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
- Exploratory efficacy endpoints:
    - Composite hematologic score

Protocol Section 13.3.2.1 (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 (ANOVA) models on hematologic parameter kinetic endpoints
- Summarization of time to nadir.
- Descriptive statistics and ANOVA of 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 13.3.2.2 (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 13.3.2.4 (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.
- ANOVA on FACT scores
- The association between composite endpoints and BOR, OS, and PFS

Protocol Section 13.5 (Exploratory Analyses)

The analysis in the section is not covered in the SAP

8. REFERENCES

Eisenhauer, E., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M. and Rubinstein, L., 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer*, *45*(2), 228-247.

Kim Y, Won S. (2013) Adjusted proportion difference and confidence interval in stratified randomized trials. *PharmaSUG; Paper SP-04*

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

Parameter	Grade				
	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.