STATISTICAL ANALYSIS PLAN
– Region 2–

Study Title:	Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated Extensive Stage Small Cell Lung Cancer
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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aRR	Adjusted Rate Ratio
AST	Aspartate Aminotransferase
[redacted]	[redacted]
ATC	Anatomical Therapeutic Classification
AUC	Area Under Curve
β-HCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BOR	Best Overall Response
BPM	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
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
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
E/P/A	Etoposide, Carboplatin, and Atezolizumab
EOI	End of Infusion
ESA	Erythropoietin Stimulating Agent
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
G1T28	Trilaciclib
GCSF	Granulocyte Colony-Stimulating Factor
HR	Hazard Ratio
ICH	International Conference on Harmonization

Abbreviation	Term
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-treat
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal Range
MAHE	Major Adverse Hematologic Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
Nadir	The Lowest Point
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
PFS2	Progression-Free Survival 2
PK	Pharmacokinetic
PLR	Platelet-Lymphocyte Ratio
PP	Per Protocol
PR	Partial Response
[redacted]	[redacted]
PT	Preferred Term
QOL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SOC	System Organ Class
SVN	Severe Neutropenia
TEAE	Treatment Emergent AE
TL	Target Lesion
TLFs	Tables, Listings, and Figures
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 G1T28-05, Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated Extensive Stage Small Cell Lung Cancer. The SAP is based on the G1T28-05 Protocol Version 3, dated 14 September 2018.

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

2. STUDY DETAILS

2.1. Study Objectives

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

Table 1 G1T28-05: Study Objectives

Primary Objective
Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression in patients with SCLC undergoing treatment with E/P/A
Key Secondary Objectives
Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A
Supportive Secondary Objectives
Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A
Evaluate the antitumor activity of trilaciclib or placebo administered in combination with E/P/A to patients with SCLC
Determine the safety and tolerability of trilaciclib or placebo administered in combination with E/P/A in patients with SCLC
Evaluate potential of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing effects on multiple lineages and current standard of care interventions to treat myelosuppression (neutrophils, RBC, platelets, lymphocytes)
Describe the PK of trilaciclib, carboplatin, and etoposide in a subset of patients; and atezolizumab in all patients
[redacted]

E/P/A = etoposide + carboplatin + atezolizumab; irRECIST = immune-related RECIST; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; PFS = progression-free survival; [redacted]; RBC = red blood cell; SCLC = small cell lung cancer

2.2. Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study of the efficacy and safety of (etoposide, carboplatin, and atezolizumab) E/P/A with trilaciclib or placebo therapy for patients with newly diagnosed extensive-stage SCLC. Approximately 100 patients will be randomly assigned (1:1 fashion) to trilaciclib 240 mg/m^2 or placebo administered IV on Days 1 to 3 with E/P/A therapy for up to four 21-day cycles (induction part). Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no). Following the completion of up to 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles, patients will proceed to the maintenance part of the study and receive atezolizumab monotherapy on Day

1 of every 21-day cycles. Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part. Treatment in both parts will continue until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. Following disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit. The study includes 3 phases: Screening Phase, Treatment Phase (induction part + maintenance part), and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes after the last Post Treatment Visit.

An independent data monitoring committee (DMC) will perform interim reviews of accumulating safety and disposition data approximately every 4 months during the Treatment Phase of the study, depending upon the enrollment rate. The first DMC meeting will occur after approximately the first 20 patients have been enrolled and completed at least 1 cycle. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

Criteria for Subsequent Cycles and Study Duration

Study drug administration will continue for up to 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles during the induction part of the study and atezolizumab monotherapy will be administered on Day 1 of every 21-day cycle during the maintenance part of the study. Study drug administration will continue until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. However, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit (see Section 11.1.4). Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons as described below.

Criteria for Starting Cycle 2 and subsequent cycles in the induction part up to Induction Cycle 4

Patients must meet all of the following criteria:

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

A delay of > 9 weeks for recovery from any toxicity related to trilaciclib or placebo + etoposide and carboplatin (E/P) in order to meet the continuation criteria will result in discontinuation of trilaciclib or placebo + E/P. A delay of > 15 weeks for recovery and management of immune-related toxicities attributed to atezolizumab (12 weeks for recovery to ≤ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to ≤ 10 mg/day) will result in discontinuation of atezolizumab. If patients meet the criteria for starting the subsequent cycle, a delay of up to 2 weeks is permitted for administrative reasons (eg, holiday, vacation, etc.);

however, a total delay of more than 9 weeks for trilaciclib or placebo + E/P, or 15 weeks for atezolizumab must be discussed with the medical monitor. [redacted]

Discontinuation or interruption of trilaciclib or placebo + E/P does not preclude continuation of atezolizumab and vice versa. For instance, if an AE is attributed to trilaciclib or placebo, etoposide, or carboplatin (eg, hematologic toxicity) during the induction part of the study; then atezolizumab may be continued while the trilaciclib or placebo + E/P are held. While the trilaciclib or placebo + E/P are held, the patient will continue to receive atezolizumab, be monitored for safety, and will begin the next trilaciclib or placebo + E/P/A-containing induction cycle after the toxicity resolves. If the AE is immune related and attributed to atezolizumab; then trilaciclib or placebo + E/P may be continued for up to 4 cycles while the atezolizumab is held.

After discontinuation of all study drugs, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, [redacted]; CBC assessment on Day 22; all Post-Treatment Visits; and the Survival Follow-up Phase of the study, which is to continue until at least 70% of the patients on the study have died. The G1T28-05 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 36 months, assuming 12 months of accrual and 24 months follow-up.
- The Survival Follow-up Phase will continue until at least 70% of the randomized patients have died.

The study scheduled assessments are presented in Table 2 below:

Table 2 Schedule of Assessments

	Screen-ing	Enroll	Induction (21-day cycles)[a]										Last Induc-tion Cycle	Maintenance (21-day cycles)[b]		Post-Treatment Visits[c]		Survival Follow-up[d]
			Induction Cycles 1 and 3					Induction Cycles 2 and 4						Maintenance Cycle 1 and Odd Cycles	Maintenance Cycle 2 and Even Cycles			
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**	**22**	**1**	**1**	**30 (+3)**	**90 (+7)**	
Informed Consent[e]	X																	
Demographics	X																	
Medical History[f]	X																	
Eligibility Eval.	X	X																
Performance Status	X		X					X						X	X	X	X	
Physical Exam	X		X					X						X	X	X	X	
Height, Weight & Vital Signs[g]	X		X		X			X		X				X	X	X	X	
Electrocardiogram	X												X					
Clinical Chemistry	X		X[h]					X[h]						X[h]	X[h]	X	X	
TSH, free T4, and free T3	X							X							X	X	X	
Hematology	X		X[i]		X	X	X	X[i]		X	X	X	X	X[i]	X[i]	X	X	
Urinalysis	X		X[h]					X[h]						X[h]	X[h]	X	X	
Pregnancy test[j]		X[j]														X	X	
Randomization[k]		X																
Tumor Assessment[l]	X[l2]											X			X	X[l1,l2]	X[l1,l2]	X[l1]
Archived Tumor Sample[m]		X																
Trilaciclib or Placebo[n]			X	X	X			X	X	X								
Carboplatin			X					X										
Etoposide			X	X	X			X	X	X								
Atezolizumab			X[o]					X[o]						X	X			
[redacted]			■					■						■	■	■	■	
PK[q] (Trilaciclib, Etoposide, Carboplatin)			X															

	Screen-ing	Enroll	Induction (21-day cycles)[a]										Last Induc-tion Cycle	Maintenance (21-day cycles)[b]		Post-Treatment Visits[c]		Survival Follow-up[d]
			Induction Cycles 1 and 3					Induction Cycles 2 and 4						Maintenance Cycle 1 and Odd Cycles	Maintenance Cycle 2 and Even Cycles			
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**	**22**	**1**	**1**	**30 (+3)**	**90 (+7)**	
Atezolizumab PK[r]			X					X							X	X	X	
Immunologic Marker[s]			X[s]											X[s]			X[s]	
[redacted]			■					■							■	■	■	
AEs[u]	X[u]		X[u]														X[u]	
Con. Medications	X		X															
Survival Follow-up[d]																		X

AE = adverse event; Eval. = evaluation; [redacted] irRECIST = immune-related RECIST; [redacted]; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = tri-iodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

a During the induction part, study drug administration (trilaciclib or placebo plus E/P/A) will continue for up to four 21-day cycles or until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re consent, study drug administration may be continued until loss of clinical benefit.

b During the maintenance part, study drug administration (atezolizumab) will continue in 21-day cycles until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re consent, study drug administration may be continued until loss of clinical benefit.

c Patients will return to the study center for post-treatment visits at 30 (+3) and 90 (+7) days after the last dose of study drug.

d Monthly phone calls will be made to each patient that is in the Survival Follow-up Phase. Patients will be followed for survival until at least 70% of the patients have died. Any anticancer therapies used will be collected.

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

f 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.

g Height will only be measured at the screening visit. Weight will only be measured at the screening visit and on Day 1 of each cycle. Body surface area calculation (based on actual body weight) will be completed on Day 1 of each cycle and vital signs obtained within 15 minutes before and after trilaciclib or placebo and E/P/A infusions. Vitals only need to be taken before the trilaciclib or placebo infusion, between each subsequent infusion, and after the last infusion on Days 1 and 3.

h Clinical chemistry (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], amylase, lipase) and urine analysis may be obtained up to 72 hours prior to the first dose of each cycle of trilaciclib or placebo + E/P/A therapy (induction part) or atezolizumab (maintenance part).

i Hematology will be obtained (hemoglobin, white blood cells (WBC) with differential, and platelet counts). Hematology may be obtained up to 24 hours prior to first dose of each cycle of trilaciclib/placebo + E/P/A therapy (induction part) or atezolizumab (maintenance part).

j For female patients of childbearing potential: serum ß-hCG at enrollment; and serum or urine ß-hCG obtained at the post-treatment visits.

k Randomization is to be done within 3 days prior to first dose of trilaciclib or placebo + E/P/A therapy, following confirmation that the patient is eligible for the study.

l For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle for 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug, 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.

l1: At the post-treatment visits at 30 (+3) and 90 (+7) days after the last dose of study drug, 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.

l2: Brain scans with contrast (by CT or MRI) to be obtained with tumor assessment at screening (within 28 days of dosing). Patients without the presence of brain metastases at screening should also have a brain scan at the end of the induction part. Patients with brain metastases at screening should have brain scans with every scheduled tumor assessment.

m Archived tumor samples should be available for banking for assessment of relevant DNA, ribonucleic acid (RNA), and protein markers, such as PD-L1 or those involved in the CDK4/6 pathway. Tumor samples may be banked for up to 10 years.

n Trilaciclib or placebo will be administered as an IV infusion in 250 mL of D5W or sodium chloride solution 0.9% over approximately 30 minutes prior to E/P chemotherapy on Days 1 to 3 of every induction cycle. If there is any volume remaining in the trilaciclib 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 trilaciclib or placebo on successive days should not be greater than 28 hours. The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours. Trilaciclib or placebo will only be administered with chemotherapy. If administration of E/P chemotherapy is discontinued, trilaciclib or placebo should also be discontinued. Chemotherapy cannot be administered until after completion of the trilaciclib or placebo infusion. If the second or third dose of trilaciclib 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, [redacted] CBC assessment on Day 22; the Post-Treatment Visits; and the Survival Follow-up Phase of the study.

o During the induction part, atezolizumab should be administered following the administration of trilaciclib or placebo, etoposide, and carboplatin.

p [redacted]

q At least 5 patients enrolled in each treatment group will have trilaciclib, etoposide, and carboplatin PK samples collected on Day 1 of Induction Cycles 1 and 3 at the time points specified.

r Blood samples will be collected from all patients predose and 30 minutes after the end of atezolizumab infusion to determine the minimum and maximum observed serum atezolizumab concentration on Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 (+3) and 90 (+7) days after the last dose of study drug.

s Peripheral blood samples will be collected at predose on Day 1 of Induction Cycle 1, Day 1 of Maintenance Cycle 1 (first cycle of maintenance part), Day 1 of Maintenance Cycle 5, and at the post treatment visit at 90 (+7) days after the last dose of study drug.

t [redacted]

u Adverse events will be recorded from the time of informed consent. AEs will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug. All AEs should be followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

2.3. Number of Patients

Overall, approximately 100 patients will be enrolled in the study. The 100 patients will be randomly assigned (1:1 fashion) to trilaciclib 240 mg/m2 or placebo administered IV on Days 1 to 3 with E/P/A therapy for up to four 21-day cycles (induction part).

The initial sample size calculations were based on a primary endpoint of OS where a sample size of 100 (1:1 treatment allocation ratio between the two groups of placebo + E/P/A and trilaciclib + E/P/A) provided 80% power to detect a hazard ratio of 0.6 using an overall type 1 error probability of 0.1 (1-sided). With the change in endpoints outlined in amendment 2, the sample size calculation is now based on demonstrating the superiority of trilaciclib + E/P/A versus placebo + E/P/A with respect to at least one of the primary endpoints. With this amendment, the overall type I error rate is now 0.025 (1-sided) and the type II error rate used to compute sample size is 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using the most conservative Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.025/2 = 0.0125 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 2 days between the treatment groups (trilaciclib + E/P/A versus placebo + E/P/A) requires 82 evaluable patients (41 per treatment arm). This implies that 88 patients need to be randomized assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for placebo + E/P/A, testing for an absolute reduction of 34% to 11% with trilaciclib + E/P/A would require a sample size of at least 100 patients (50 per treatment arm). Assuming a 95% evaluability rate, at least 106 patients need to be enrolled to complete the study. Therefore, the final adjusted sample size is 106 to account for the evaluation of 2 primary endpoints.

All calculations were carried out using the POWER procedure in SAS® version 9.4.

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

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

3.1.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set includes all randomized patients. Analyses using the ITT will be conducted on the basis of the assigned treatment. The ITT is the primary analysis set for all efficacy analysis.

3.1.2. Modified ITT Analysis Set

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

3.1.3. Safety Analysis Set

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

3.1.4. Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set and may also be used to analyze select endpoints. The criteria for inclusion in the PP analysis set will be based on study drug administration and major protocol deviations, and it will be finalized and documented prior to unblinding patients in the study.

It will include only those patients who have no key protocol deviations (as described in Section 3.2) and who received the treatment to which they were randomized. For any patients who received the wrong treatment during any 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.

3.1.5. Response Evaluable Analysis Set

The Response Evaluable Analysis Set will include all patients who are in the mITT and (1) have at least 1 post-baseline tumor assessment, (2) discontinued treatment because of clinical progression, or (3) died due to disease progression before their first postbaseline tumor scan. The response evaluable analysis set will be used for analyses of tumor response.

3.1.6. Pharmacokinetics (PK) Analysis Set

The PK Analysis Set will not be used for any analyses described in this SAP. Rather the PK analyses and the PK Analysis Set will be described in a separate document.

3.2. Protocol Deviations

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

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

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

If the wrong treatment is administered to a patient, and the reason for the incorrect treatment is documented, this will be noted in the CSR and the patient's data included in the Safety Analysis Set based on the actual treatment received. All major protocol deviations will be reviewed in a data review meeting to classify protocol deviations as non-key or key, and to discuss the potential impact on statistical analysis. This will be documented in a note to file prior to database lock and unblinding.

4. PROSPECTIVELY DEFINED ANALYSES

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

To capture the potential for multilineage 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 and 6.2.7 with the multiplicity adjustments described in Section 6.2.7.1.4.

Table 3 Prospectively Defined Analyses

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

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

5. PRIMARY AND SECONDARY ENDPOINTS

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

Term	Definition
Severe Neutropenia (SVN)	ANC lab value that meets the common terminology criteria for adverse events (CTCAE) criteria for ≥ Grade 4 toxicity
Cycle baseline	The last non-missing value within the window starting from 3 days prior to the date/time of study drug 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 induction cycle (where no subsequent maintenance cycle is given), the end of cycle will be defined as Day 36 after the first dose of the cycle. For the last maintenance cycle, the end of cycle will be defined as Day 30 after the first dose of the cycle.
Start of cycle	Day 1 of each cycle starts with the administration of study drug(s) (etoposide, carboplatin, atezolizumab, or trilaciclib)
Start of study	Date of randomization
Study baseline	The last non-missing value prior to, or on the date of administration of study drug(s) (etoposide, carboplatin, atezolizumab, 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.
Induction treatment period	Between the date of randomization and end of cycle for the last Induction cycle.
Maintenance treatment period	Between the date of Day 1 of the first maintenance cycle and end of cycle for the last Maintenance cycle.
Overall treatment period	Between the date of randomization 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

Unless otherwise specified, all primary and key secondary efficacy endpoints will be evaluated and derived for the induction treatment period.

5.1.1. Primary Endpoints

5.1.1.1. Occurrence of Severe (Grade 4) Neutropenia

For the induction treatment period, the total number of SVN events is the number of induction cycles where at least one ANC value is $< 0.5 \times 10^9$/L. For example, if Cycle 2 has two ANC values that are both $< 0.5 \times 10^9$/L, this only counts as one event. If a patient did not have any SVN events, the value of 0 will be assigned to that patient. The number of induction cycles without SVN is calculated as total number of induction cycles received – total number of induction cycles with SVN. Unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

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

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

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

5.1.1.2.1 Strategy 1: Without Imputation of Missing ANC Values

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

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

5.1.1.2.2 Strategy 2: Without Imputation, Censoring Unresolved SVN

Within each cycle, DSN (days) is defined as the number of days from the date of first ANC value of $<0.5 \times 10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5 \times 10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5 \times 10^9$/L and (2) no other ANC values $<0.5 \times 10^9$/L occur between this day and end of cycle. If no SVN occurs, then the cycle is not used in this analysis. The following censoring rules will be applied in the calculation:

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

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

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

5.1.1.2.3 Strategy 3: With Imputation of Missing ANC Values

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

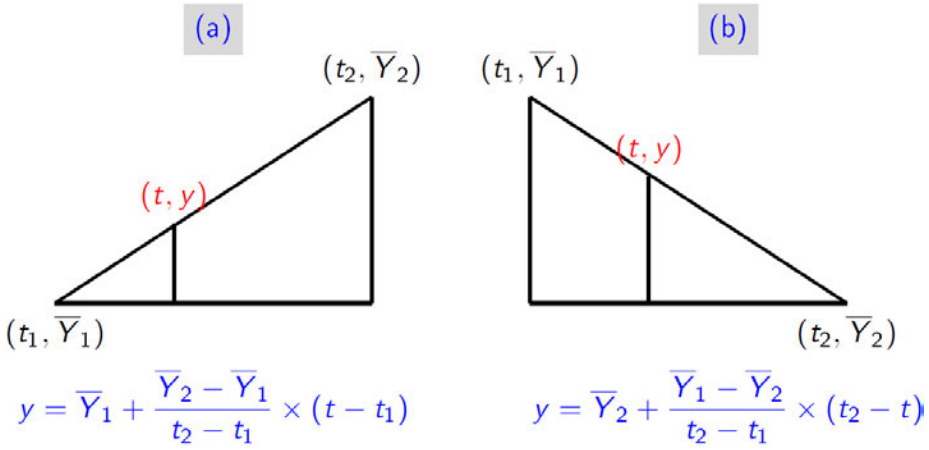
To impute the missing daily ANC value, the following algorithms will be applied in the calculation,

(1) Rules of imputation of missing values at Day 2 of a cycle:

- The ANC before and after the missing day was $\geq 0.5 \times 10^9$/L: the day is ignored as a potential day of severe neutropenia.
- If at either neighboring days the ANCs were $< 0.5 \times 10^9$/L, and both are non-missing, then the missing day is set to severe neutropenia.
- If any of the neighboring days were also missing, severe neutropenia cannot be determined, and the data remains missing.

(2) Missing ANC values for Days 3-8 in each cycle will be imputed using linear interpolation, any recorded measurement will not be replaced. The missing values for Day 3 and Day 8 may be potentially imputed with this algorithm.

Figure 1 Graphical Demonstration of Linear Interpolation



Note: The slopes are calculated for each treatment group, where $\bar{Y}_1$ and $\bar{Y}_2$ are the mean of ANC values at relevant timepoint. For a time interval, e.g. interval of Day 1 and Day 8 (inclusive), $\bar{Y}_1$ is the average of the earliest point in the interval and t_1 is the average of the earliest day in the interval. Similarly, $\bar{Y}_2$ is the average of the latest point in the interval and t_2 is the average of the latest day in the interval.

- If there are at least two assessments within the interval of Day 3 and Day 8 (inclusive), calculate the slope between the first available ANC value and last available ANC value:
  - If the sign of slope agrees with the sign of slopes calculated from its treatment group, the interpolation will be conducted to appropriate schemes as demonstrated in Fig.1 (a) and Fig. 1(b);
  - If the sign of slope does not agree with the sign of slopes calculated from its treatment group, the interpolation will be done within the patient by using the calculated slope from the observed values.
- If there is only one assessment within the interval of Day 3 and Day 8 (inclusive),
  - If the ANC value is $< 0.5\times10^9$/L, then the subsequent missing days will be set to this value;
  - If ANC value is $\geq 0.5\times10^9$/L, SVN cannot be determined, and the data remains missing.
- If there is no assessment within the interval of Day 3 and Day 8 (inclusive), SVN cannot be determined, and the data remains missing.

(3) A similar algorithm as in (1) will be performed to impute missing ANC values for Days 9-15 in each cycle using linear interpolation. Day 8 will be used as the earliest date in the

calculations only if it is recorded; it will be interpolated in this interval. Any other recorded measurements will not be replaced.

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

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

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

5.1.2. Key Secondary Endpoints

5.1.2.1. Occurrence of RBC Transfusions

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

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

5.1.2.2. Occurrence of GCSF Administrations

Administration of GCSF is collected throughout the induction treatment period. Those cycles 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 induction treatment period, the total number GCSF administrations is the number of induction 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 induction cycles where GCSF was NOT given is calculated as total number of induction cycles received – total number of induction cycles where GCSF was administered.

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

5.1.2.3. All-Cause Dose Reductions

Dose reductions are not permitted for trilaciclib or atezolizumab. Dose reductions for E/P are derived from changes in the protocol-specified dose on the dosing page and correspond to the reductions for toxicity specified in the protocol.

No more than 2 dose reductions of E/P in total are allowed for any patient. Simultaneous reduction in the doses of etoposide and carboplatin will count as 1 dose reduction. For more details see Section 5.2.1.4.

5.1.2.4. Overall Survival

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

Overall survival is calculated as the time (months) from date of randomization 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 date of randomization will have their survival time censored at date of randomization. OS will not be censored if a patient receives other anti-tumor treatments after the study drugs.

5.1.3. Supportive Secondary Endpoints

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

As a composite measure of trilaciclib effect, MAHE is based on a combination of individual components specified in Table 4, which also include details about the derivation or data source for each component. For each component of composite MAHE, its number of events is derived as the number of episodes with a unique start date during the induction treatment period between the date of randomization and the end of the last induction cycle (i.e. last cycle of placebo or trilaciclib plus E/P/A). A patient with absence of an episode will be assigned a value of 0 to the number of events for this component. Then, the total number of MAHE during the induction treatment period is obtained as the summation over all components of composite MAHE during the induction treatment period.

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

Seq #	Component of MAHE	Details
1	All-cause hospitalizations	Each hospitalization is captured in the AE data of the electronic database. Each recorded Preferred Term (PT) with a unique start date will be counted as an event, e.g. if a patient is hospitalized and several preferred terms are attributed to that hospitalization with the same start date, then the event is only counted once. The event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
2	All-cause dose reductions	Detailed in Section 5.1.2.3
3	Febrile neutropenia	Detailed in Section 5.1.3.10
4	Prolonged severe (Grade 4) neutropenia (duration > 5 days)	Detailed in Section 5.1.1.2.1. Each cycle with a duration greater than 5 days will be counted as an event with the date of the first grade 4 lab value defined as the start date for the time-to-first event analysis.

Seq #	Component of MAHE	Details
5	RBC transfusion on/after 5 weeks	Detailed in Section 5.1.2.1

A patient with absence of any episode of MAHE will be assigned a value of 0 for the total number of MAHE. Additionally, a sensitivity analysis will be done for dose reductions and RBC transfusions on/after 5 weeks, that excludes patients who do not start a second cycle of treatment.

Time to first occurrence of a MAHE will be used as a sensitivity analysis in support of the total number of MAHE. It is defined as the first time to observe an event among all the components, starting from the date of randomization. Therefore, for a patient with presence of MAHE, time (months) to first occurrence of a MAHE will be the minimum among the 5 potentially derived durations (i.e. calculated as (date of first occurrence of a MAHE component event – date of randomization + 1)/30). A patient without any MAHE will be censored at the end of the last cycle (i.e. last cycle of placebo or trilaciclib), death, end of study, or date of last contact, whichever is earlier.

5.1.3.1.1 All-Cause Hospitalizations

See Section 5.1.3.1.

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

See Section 5.1.3.1.

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

For tumor assessment, all sites of disease will be assessed radiologically by CT or MRI at screening, every 6-9 weeks thereafter as determined by the protocol, until the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. At each tumor assessment visit, the overall visit response by RECIST will be determined two ways: (1) derived programmatically using the information from target lesions (TL), non-target lesions (NTLs) and new lesions as entered into the eCRF, and (2) by the investigator and collected in the eCRF.

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

5.1.3.2.1 Target Lesions (TLs)

Measurable disease is defined as having at least one measurable lesion at baseline 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 5 gives definition of TL visit responses.

Table 5 Definition of TL Visit Responses

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

Rounding of TL data

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

Missing TL data

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

TL too small to measure

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

Lesions that split

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

Lesions that merge

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

Change in method of assessment of target lesions

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

5.1.3.2.2 Non-Target Lesions (NTLs) and New Lesions

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

Table 6 Definition of NTLs Visit Responses

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

New lesions

New lesions (target or non-target) will be identified via a separate eCRF page. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL responses.

5.1.3.2.3 Time Point Response (TPR)

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

Table 7 Evaluation of Time Point Response: Patients with Baseline Target Lesions

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

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

At each visit, patients will be programmatically assigned a RECIST Version 1.1 TPR of CR, PR, SD, PD or NE depending on the status of their disease compared to baseline and previous assessments as discussed in the Sections 5.1.3.2.1 and 5.1.3.2.2.

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. Within a

grouped timepoint, if there are multiple assessments on different dates for the *same* target lesions, the last assessment will be used.

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

BOR will be determined using TPRs up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1; 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 8. For data-driven scenarios which may not be covered by Table 8, the BOR will be reviewed and determined by the medical advisors and statisticians prior to locking the database.

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

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

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

Both ways of assigning BOR will be implemented.

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

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

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

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not available, ORR = Objective Response Rate

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

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

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

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

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

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

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

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

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

Duration of Response (DOR) is the time between first response by RECIST Version 1.1 of CR or PR and the first date that progressive disease is documented by RECIST Version 1.1, or death. Patients who do not experience PD or death will be censored at the last tumor assessment date. Only those patients with confirmed responses will be included in this analysis. Censoring will follow the rules outlined below for PFS in Section 5.1.3.2.5.

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

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

5.1.3.2.5 Progression-free Survival

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

Hence, progression-free survival (PFS) is defined as the time (months) from date of randomization until date of documented disease progression or death due to any cause, whichever comes first. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

PFS will be calculated using derived responses and progression by RECIST Version 1.1 (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 9.

Table 9 Assignment of Progression or Censoring Based on Radiological Assessment

Situation	Date of Progression or Censoring	Outcome
No progression - treatment not started	Date of randomization	Censored
No progression	Date of last adequate radiological disease assessment	Censored
Treatment discontinuation for reasons other than disease progression	Date of last adequate radiological disease 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

Situation	Date of Progression or Censoring	Outcome
Disease progression per RECIST Version 1.1	Date of the first reported progression	Progressed
Death without a PD	Date of death	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.

5.1.3.3. Occurrence of Grade 3 and 4 Hematologic Toxicities

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

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

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

5.1.3.4. ANC Nadir by Cycle

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

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

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

5.1.3.6. Occurrence of Erythropoiesis Stimulating Agent (ESA) Administrations

Administration of ESAs is collected throughout the induction treatment period. Those induction 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 induction treatment period, the total number of ESA administrations is the total number of induction cycles in which there is at least one ESA dose administered; If a patient did not receive an ESA, the value of 0 will be assigned to that patient. The number of induction cycles

where ESAs were NOT given is calculated as total number of induction cycles received – total number of induction cycles where ESAs were administered.

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

5.1.3.7. Occurrence of IV Antibiotic Uses

IV antibiotic administration is collected with concomitant medications which are coded using World Health Organization Drug Dictionary (WHO-DD) Version Sep2017. The criteria for identifying an IV antibiotic administration event is

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

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

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

5.1.3.8. Occurrence of Infection Serious Adverse Events (SAEs) and Pulmonary Infection SAEs

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

Each infection SAE with a unique start date during the induction treatment period will be defined as separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

Any occurrence of an infection SAE during the induction 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.

5.1.3.9. Occurrence of Pulmonary Infection SAEs

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

Table 10 PT List for Grouping Pulmonary Infection AEs

Category	Preferred terms
Pulmonary Infection AEs	Bronchiolitis
	Bronchitis
	Influenza
	Pneumonia
	Pneumonia bacterial
	Respiratory tract infection
	Upper respiratory tract infection
	Viral upper respiratory tract infection

Each pulmonary infection SAE with a unique start date during the induction treatment period will be defined as separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

Any occurrence of a pulmonary infection SAE during the induction 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.

5.1.3.10. Occurrence Febrile Neutropenia

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

Each febrile neutropenia event with a unique start date during the induction treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

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

[redacted]

[redacted]

5.2. Safety Endpoints

5.2.1. Chemotherapy Exposure Endpoints

5.2.1.1. Duration of Exposure

Duration of exposure will be calculated for the overall treatment period as well as separately for the induction treatment period and the maintenance treatment period. Note that Duration of exposure will be different than Duration of the treatment period defined elsewhere, and it will only apply to exposure summaries.

Induction period duration of exposure (days) = Day 1 of last induction cycle – Cycle 1 Day 1 of induction phase + 21.

Maintenance period duration of exposure (days) = Day 1 of the last maintenance cycle – Cycle 1 Day 1 of maintenance phase + 21.

Overall period duration of exposure (days) = Day 1 of the last cycle (either maintenance or induction) – Cycle 1 Day 1 of induction phase + 21.

5.2.1.2. Number of Cycles Received

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

5.2.1.3. Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 12. All doses, including unscheduled doses, will be used in the applicable parameter calculations. For trilaciclib/placebo, etoposide, and carboplatin, these drug specific calculations will be for induction period exposure only. For atezolizumab they will be for induction, maintenance, and overall exposure periods.

Table 12 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Trilaciclib	Etoposide	Carboplatin	Atezolizumab*
Dosing schedule per protocol	240 mg/m^2 IV on Days 1,2,3 of a 21-day cycle	100 mg/m^2 IV on Days 1,2,3 of a 21-day cycle	AUC 5 IV on Day 1 of a 21-day cycle	1200 mg IV on Day 1 of a 21-day cycle
Dose by cycle	Total dose administered (mg) /most recent BSA (m^2) [(mg/m^2)]	Total dose administered (mg) /most recent BSA (m^2) [(mg/m^2)]	Total dose administered on Day 1 (Prescribed AUC and actual dose in mg)	Total dose administered (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)	Sum of the doses administered to a patient in the duration of exposure, (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]	Cumulative Dose (mg) / (duration of exposure / 7) [(mg/week)]
Relative dose intensity (%)	100 * [Dose intensity (mg/m^2/week) / (720 /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)]	100 * [Dose intensity (mg/week) / (1200 /3 (mg/week)]
Relative Dose (%)	100 * [Cumulative dose (mg/m^2) / (720 × 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)]	100 * [Cumulative dose (mg) / (1200 × number of cycles (mg)]

AUC = area under curve; BSA = body surface area; IV = intravenous.
*Atezolizumab will have these calculated for the induction, maintenance, and overall periods.

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

- After Cycle 1, patients need to meet pre-specified laboratory parameter criteria before initiating Cycle 2 and each subsequent cycle of chemotherapy. A "Cycle Day Status" page asks if the cycle was delayed. If the start of the current cycle was delayed (the site

answers "Yes"), this will be counted as a delay. Reason for delay is not collected. Delays will be calculated over the induction, maintenance, and overall periods.

- Missed doses are identified on the dosing page of each study drug based on the question "Was the dose given?". The missed dose information will be obtained for each study drug. For a study drug, if the last record of response to question "Was the dose given?" is No, it will not be considered as a missed dose but instead considered to be end of treatment if both criteria below are met
  - No other study drugs are given on the same day, and
  - No study drugs are given subsequently.

  The reasons for missed doses will be summarized in the following categories: (1) Hematological toxicity, (2) Non-hematological toxicity, and (3) Other.
- Dose reductions are not permitted for trilaciclib or atezolizumab.
- Dose reductions for carboplatin and etoposide are determined by comparing the actual dose on the respective drug administration pages between the current cycle and the previous cycle. A window of 10% around both etoposide and carboplatin doses will be used to check for dose reductions. They occur in the following order:
  - 1st Reduction: Etoposide dose reduced from 100 mg/m^2 to 75 mg/m^2, Carboplatin dose reduced from AUC 5 to AUC 4.
  - 2nd Reduction: Etoposide dose reduced to 50 mg/m^2, Carboplatin dose reduced to AUC 3.

  No more than 2 dose reductions of E/P in total are allowed for any patient. Toxicity that requires dose reduction more than twice will lead to discontinuation of trilaciclib or placebo + E/P therapy; discontinuations will not be counted as a dose reduction. All dose reductions for toxicity are permanent, and no dose increases are allowed when dose reductions are made for toxicity.
- Dose interruptions for all drugs are also captured on the dosing page and will be summarized for each study drug.

5.2.2. 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 up to 30 days after the last dose of study treatment. SAEs and AESI will be collected through 90 days after the last dose of study drug. AEs are graded by investigator according to CTCAE, Version 4.03.

For the induction treatment period, TEAE analyses will include all AE's that started on or after the first dose of study drugs and up to the date of first dose of atezolizumab in the maintenance period. If the subject did not enter the maintenance period, then AEs up to the first dose of the last cycle in the induction period + 36 days (inclusive) will be considered TEAE.

For the maintenance treatment period, TEAE analyses will include all AE's that started on or after the first dose of atezolizumab in the maintenance period through the last dose of the maintenance period + 30 days.

For TEAEs that are designated as SAEs or AESIs, data will be summarized through the last dose of atezolizumab + 90 days.

TEAEs will be summarized overall and by the period in which they occur.

Other AE variables include drug-related AEs, AEs leading to study drug discontinuation or study withdrawal, AEs leading to death, SAEs, and atezolizumab AESIs.

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 13 outlines those terms that will be consolidated.

Table 13 Preferred Terms to Be Consolidated

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

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

Infusion reaction AEs are signified in the study drug administration forms and that information is linked to the details entered on the AE page to distinguish those for a subset summary. Additionally, a summary from the AE data only will be presented for those records where "INFUSION RELATED REACTION" is a preferred term. The event terms are coded using the MedDRA Version 20.1.

5.2.3. Vital Signs

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

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

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 14:

Table 14 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
Oxygen Saturation	≤ 90%	n/a
Pulse	≥ 120 bpm	Increase ≥40 bpm
	≤ 50 bpm	Decrease ≥40 bpm
Weight	n/a	Change ≥10%

bpm = beats per minute

5.2.4. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 15 will be measured.

Table 15 Laboratory Assessment

Lab Category	Lab tests
Hematology	hemoglobin, white blood cell (WBC), platelet counts, ANC, ALC, Monocytes, Bands, Basophils, and Eosinophils.
Chemistry	albumin, Alkaline Phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), sodium, and Blood Urea Nitrogen (BUN), Lipase, Amylase, Thyrotropin, Free Thyroxine, and Free Triiodothyronine
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. The urinalysis results will not be summarized; they will only be included in listings.

For hematology parameters, if absolute counts are not provided, they will be derived from the differential counts; the normal ranges will be left missing in those cases. The formula used will be: Differential value * Leukocyte value from the same sample.

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

5.2.5. Electrocardiograms

Electrocardiogram (ECG) parameters include heart rate, PR interval, RR 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 will be listed but not summarized.

Collected QTcB and QTcF will not be used, but will instead be derived from the QT and RR (converted from collected msec to sec) interval based on the following formulas:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

If QT and/or RR is missing, the QTcB and QTcF will be left as missing.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 16. ECG results are interpreted as clinically significant or not clinically significant.

Table 16 Potentially Clinically Significant Criteria for ECG

ECG Parameter	Criterion value
Heart Rate	>120 bpm
	<50 bpm
PR Interval	≥ 210ms
RR Interval	> 1200ms
	< 500ms
QRS Interval	≥ 120ms
	≤ 50ms
QT Interval	≥ 500ms
	≤ 300ms
QTcB, QTcF Intervals	≥ 500ms
	≥ 480ms
	≥ 450ms
	≤ 300ms
	Change from baseline ≥ 30 ms
	Change from baseline ≥ 60 ms

5.2.6. Physical Examination

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

6. ANALYSIS METHODS

6.1. General Principles of Analysis

6.1.1. General Methodology

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

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

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings. Upon completion, all SAS® programs will be validated by an independent programmer within the staff of the third-party vendor doing the primary analysis. The validation process will be used to confirm that statistically valid methods have been implemented and that all data transformations 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 17.

Table 17 Treatment Display in TLFs

Treatment Group	Treatment Description in Data Display
1	Placebo + E/P/A
2	Trilaciclib 240 mg/m^2 + E/P/A

All statistical tests will be presented at a two-sided .05 alpha level unless otherwise specified. The primary comparison will be conducted between placebo group and Trilaciclib group. Where appropriate, model-based point estimates, together with their 95% CIs will be presented along with the two-sided p-values for the tests. P-value will be presented to 4 decimal places, if the p-value <0.0001, the value will be presented as "<0.0001".

For continuous data, the same number of decimal places as in the raw data will be presented when reporting mean, median, minimum and maximum; one more decimal place than in the raw data will be presented when reporting standard deviation and standard error (SE). The derived variables will be presented with 1 decimal place. Percentages will be reported with 1 decimal 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%." Any rounding will be done after all calculations are made.

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 5.2.2 for the method of imputation of missing AE onset and stop date and Section 6.2.5 for the method of imputation of missing concomitant onset and stop dates.

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

For the efficacy analyses, missing data will be excluded except for the sensitivity analyses noted in Section 6.2.7.1.5.

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 occur. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 18. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patient listings.

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

Only induction treatment cycles will have windowed visits. For maintenance treatment cycles, nominal visits will be used as all assessments are scheduled for Day 1 of each cycle.

Table 18 Visit Windowing

	Induction Cycles					Post-treatment [d]	Post-Treatment Visit + 60 days [e]
Visit	**C1D1**	**C1D3**	**C1D8**	**C1D15**	**EOC**		
Scheduled Day [a]	1	3[e]	8	15	22		
Clinical Chemistry [b]	Day -3 to 1				2 to EOC	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.
Hematology [c]	Day -1 to 1	1 to 5	6 to 11	12 to 18	19 to EOC	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.

[a] The scheduled day is relative to the Day 1 of each cycle.
[b] Clinical chemistry may be obtained up to 72 hours prior to the first dose of each cycle.
[c] Hematology may be obtained up to 24 hours prior to dosing on Days 1 and 3 of each cycle, Days 8 and 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.
[d] 30 ± 3 days after the last dose of study drug. Only windowing for subjects that have completed treatment.
[e] 60 ± 7 days after the post-treatment visit. Only windowing for subjects that have completed treatment

6.1.4. Adjustment for Covariates

Patient randomization was stratified by ECOG performance status (0 or 1 vs. 2) and presence of brain metastases (Yes vs. No). The efficacy analyses will use the stratification factors as covariates in statistical models.

6.2. Analysis Methods

6.2.1. Patient Disposition

A summary table will be generated to provide the following by treatment group:

- Number of patients screened
- Number and percentage of screening failures
- Reason for screening failure
- Number of patients dosed
- Number of patients randomized
- Number of patients randomized and not dosed

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/ongoing for each study drug)
- Reason for study drug discontinuation (for each study drug)
- Number of patients going into Survival follow-up
- Number of patients continuing into Maintenance period
- Number and percentage of patients who discontinued the study
- Reason for study discontinuation
- Death and reason for death

6.2.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics, such as age at informed consent date, age groups (18-65, >65-75, >75), gender, race, ethnicity, country, screening vital signs (body weight, height, BMI, BSA), ECOG status, presence of brain metastases, and smoking history (never smoker, former smoker and current smoker), will be summarized and listed.

6.2.3. Disease Characteristics

Disease characteristics including diagnosis confirmation by neuroendocrine markers, stage at diagnosis, site from which diagnostic sample was obtained, and baseline LDH will be summarized and listed. Date of SCLC diagnosis, and date of extensive stage diagnosis will be listed only.

6.2.4. Medical/Surgical 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/surgical history within each SOC and PT will be provided by treatment group. 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 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 the month will be used to complete the end date of the medication;
- If the day and month parts of the medication end date are missing, December 31st will be used to complete the onset date of the medication;
- If the medication end date is completely missing and the onset date of the medication occurs after the date of the first dose of study drug, 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. Radiotherapy and Subsequent Anti-Cancer Therapy

The prior and subsequent radiotherapy (Yes or No), site and reason will be summarized by treatment group and listed.

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

The subsequent anti-cancer therapy 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. Additionally, anti-cancer therapies will be grouped into lines of treatment and the number of subsequent lines of therapy will be summarized categorically. Best response to treatment will also be summarized. The data will be presented in a patient listing. 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. Data will be summarized using descriptive statistics and the between treatment comparison (trilaciclib vs placebo), will be performed only for the primary and secondary endpoints outlined in Sections 5.1.1 – 5.1.3. The comparisons between trilaciclib vs. placebo will be built into the multiplicity adjustment described in Section 6.2.7.1.4, the adjusted one-sided p-values will be reported and be the basis for the study drug efficacy conclusion and claim at the significance level of one-sided 0.025. However, for these comparisons, all statistical tests will be conducted at a two-sided .05 alpha level unless otherwise specified. Where appropriate, model-based point estimates, together with their two-sided 95% CIs will be presented along with the two-sided p-value for the test unless otherwise specified. Graphical presentation of efficacy results will be performed as needed.

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

6.2.7.1 Primary and Key Secondary Efficacy Analyses

6.2.7.1.1 Primary Efficacy Analyses

The primary efficacy endpoint, occurrence of SVN, is a binary response variable (Yes, No). It will be summarized using descriptive statistics by treatment group and will be analyzed to compare trilaciclib and placebo using modified Poisson regression (Zou, 2004) to account for the variable duration of the induction treatment period for each patient. The model will include baseline ANC as a covariate, the stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. The logarithm transformation of number of induction cycles will be included as an offset variable in the modeling. The two-sided p-value, adjusted rate ratio (aRR) (trilaciclib vs placebo) and its 95% CIs will be presented.

For the other primary efficacy endpoint, DSN in Cycle 1 based on Strategy 1 in Section 5.1.1.2.1, treatment difference will be evaluated using a nonparametric analysis of covariance

(ANCOVA) (Stokes 2012). The nonparametric ANCOVA will include study baseline ANC value as covariate, stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. A two-sided p-value will be generated from this model. Along with the descriptive statistics, the mean difference and Hodges-Lehmann estimate of median difference between the two treatment groups, together with its 95% CIs will be provided.

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

6.2.7.1.2 Key Secondary Efficacy Analyses

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

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

All-cause dose reductions will be analyzed to compare trilaciclib and placebo using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. The logarithm transformation of number of induction cycles will be included as an offset variable in the modeling. The two-sided p-value, aRR (trilaciclib vs placebo) and its 95% CIs will be presented.

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

6.2.7.1.3 Key Secondary OS Analysis

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

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

6.2.7.1.4 Multiplicity Adjustments

The clinical trial evaluates the objectives defined in terms of the comparison of trilaciclib + E/P/A versus placebo + E/P/A on the primary and key secondary myelosuppression efficacy endpoints in Sections 5.1.1 and 5.1.2.

The multiplicity problem includes the following 5 hypotheses of no effect:

- Hypothesis H_1. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H_2. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of severe (Grade 4) neutropenia.
- Hypothesis H_3. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for all-cause dose reductions in the MAHE composite.
- Hypothesis H_4. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of RBC transfusions on/after Week 5 on study.
- Hypothesis H_5. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of G-CSF administration.

These 5 hypotheses can be grouped into 3 families:

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

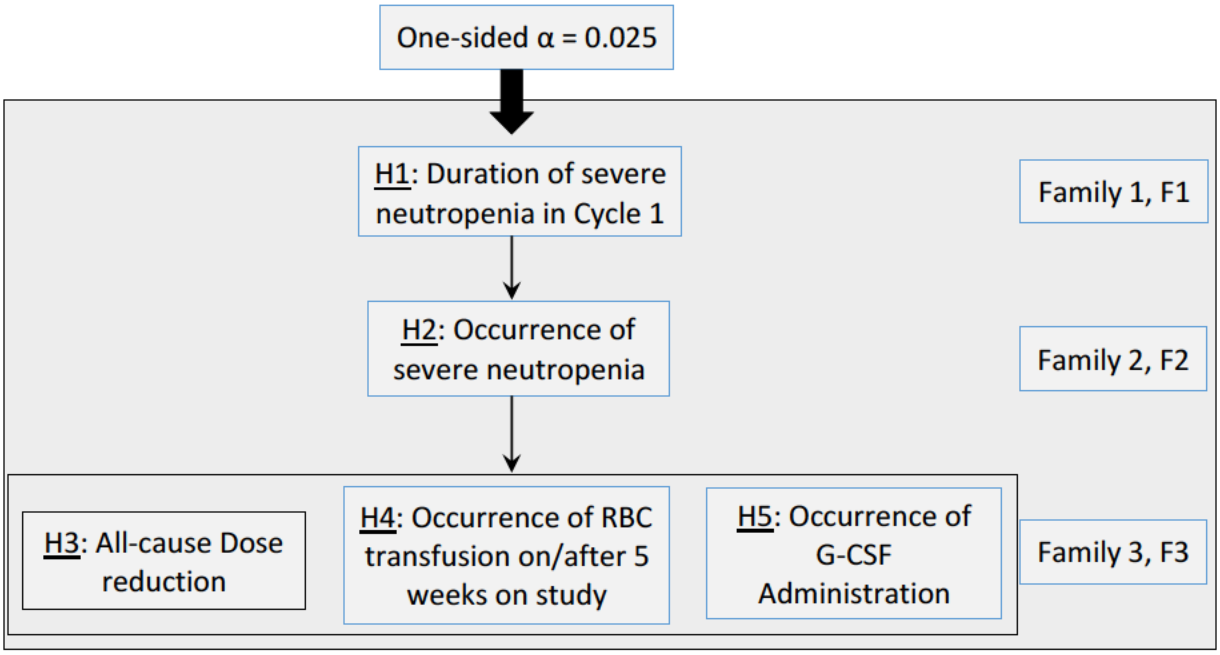
The 1-sided p-values for these 5 comparisons will be used for the multiple testing procedure.

A Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the 5 null hypotheses in the strong sense at a 1-sided α=0.025 level, and it satisfies the positive dependence condition at the 1-sided setting. The procedure is built using the mixture methodology developed in Dmitrienko and Tamhane (2011) and accounts for the logical restrictions among the 5 hypotheses displayed in

Figure **2** by performing multiplicity adjustments in three steps. The logical restrictions can be achieved by defining the parallel set and serial set for each individual hypothesis based the tree-structured procedure introduced by Dmitrienko et al (2007).

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

Figure 2 Graphical Display of the Hochberg-based Gatekeeping Procedure



The logical restrictions in the Step 1 and Step 2 contain only one single hypothesis, and the Step 3 has three hypotheses H3, H4, H5, though the testing procedure can be broadly considered as a fixed sequence procedure, its implementation can be performed through the framework of Hochberg-based gatekeeping procedure as described in detail below.

The regular Hochberg test is defined in Dmitrienko et al. (2009) and the truncated Hochberg test is defined in Dmitrienko, Tamhane and Wiens (2008). The decision rules used in the regular and truncated Hochberg tests will be detailed in the following. In general terms, the truncated version of the Hochberg test is defined as a convex combination of the regular Hochberg and Bonferroni tests. An important parameter of the truncated Hochberg test is the truncation parameter γ which ranges between 0 and 1. If the truncation parameter γ is set to 0, the truncated Hochberg test simplifies to the Bonferroni test. On the other hand, if the truncation parameter γ is set to 1, the truncated Hochberg test is identical to the regular Hochberg test. The truncated Hochberg test satisfies the separability condition (Dmitrienko, Tamhane and Wiens, 2008) if the truncation parameter γ is strictly less than 1. This condition ensures that in each step of the testing algorithm the error rate can be transferred to the next step provided at least one comparison is significant in the current step without inflating the overall type I error rate (Huque, 2016; FDA, 2017).

Testing algorithm

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

Decision rules

The aforementioned 5 hypotheses are grouped into 3 families:

- Family 1 (F_1) includes the hypothesis H_1.

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

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

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

where the index sets are defined as $N_1 = \{1\},\ N_2 = \{2\}, N_3 = \{3,4,5\}$. Let t_i and p_i denote the test statistic and 1-sided p-values associated with the hypotheses, respectively. Let α denote the global familywise error rate, i.e., one-sided $\alpha = 0.025$.

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

$$I \subseteq N\ = \{1,\ldots,5\}$$

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

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

Step 1: Define p-values for subset intersections

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

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

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

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

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

Here γ_1 is the pre-specified truncation parameter in Family 1. Choosing a larger value of γ_1 improves the power of comparisons in Family 1, and γ_1 is set to 0.5.

Further, let n_2 denote the number of hypotheses included in the index set I_2. If $n_2 > 0$, consider the hypotheses in the index set I_2 and remove the hypotheses that are not consistent with the logical restrictions defined in

Figure **2**. Let m_2 denote the number of hypotheses remaining in the index set I_2 after this logical restriction operation. If $m_2 > 0$, let

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

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

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

where γ_2 is the pre-specified truncation parameter in Family 2, which plays the same role as γ_1 in Family 1, and γ_2 is set to 0.5.

Finally, let n_3 denote the number of hypotheses included in I_3. If $n_3 > 0$, remove the hypotheses that are not consistent with the logical restrictions defined in

Figure **2**. Let m_3 denote the number of hypotheses remaining in the index set I_3 after this logical restriction operation. If $m_3 > 0$, let

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

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

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

Step 2: Define overall p-value

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

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

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

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

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

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

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

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

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

where $b_3 = 1$.

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

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

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

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

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

As shown in Dmitrienko and Tamhane (2011), the resulting test for the intersection corresponding to the index set I is an α-level test. This implies that the Hochberg-based

gatekeeping procedure controls the global familywise error rate in the strong sense at a one-sided $\alpha = 0.025$.

Multiplicity-adjusted p-values

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

Regular and truncated Hochberg tests

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

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

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

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

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

6.2.7.1.5 Robustness of Primary and Key Secondary Efficacy Analyses

A binary response variable (Yes, No) will be analyzed to compare trilaciclib and placebo using stratum-adjusted method to account for ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No) as the stratification factor. The adjusted proportion difference (trilaciclib vs placebo) and its 95% CIs will be calculated using Cochran-Mantel-Haenszel (CMH) weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method. Additionally, three sets of sensitivity analysis will be conducted to evaluate the robustness of the results from primary or key secondary analyses for a binary response variable (Yes, No).

(i) For patients who die during the induction treatment period (up to 30 days after last dose in induction period) without experiencing an event, Yes will be assigned to the variable.

(ii) After the imputation from (i), a worst-comparison analysis will be done to establish a stringent boundary of the treatment effect. Patients who die during the induction treatment period will still be set to Yes, and patients who do not complete 4 induction cycles and do not experience an event will then be imputed. If the patient is from the placebo group, No will be assigned to the variables, Yes will be assigned to the trilaciclib group.

(iii) After the imputation from (i), a tipping-point analysis (Yan et al,. 2009) will be performed by assigning the response to the variable for patients who do not complete 4 induction cycles and do not experience an event.

The tipping-point analysis assumes all possible combinations of numbers of Yes and No for the missing responses (defined as patients without an event who have less than 4 induction cycles) in the trilaciclib and placebo groups. For example, let n_t be the number of randomized trilaciclib patients with missing response and n_c be the number of randomized placebo patients with missing responses. For the trilaciclib patients with missing values, there are $n_t + 1$ possible assumptions for number of No (i.e. 0, 1, 2, …, to n_t); for the placebo patients with missing values, there are $n_c + 1$ possible assumptions for number of No. Therefore, there are total of $(n_t + 1) \times (n_c + 1)$ possible combination of assumptions for number of No and Yes for the trilaciclib and placebo patients with missing responses. The un-stratified exact CMH method will be performed on the available responses with each of these $(n_t + 1) \times (n_c + 1)$ assumptions and will be summarized. A figure will be presented with points representing each possible combination where the significant p-value 'tips' to greater than a one-sided 0.025, which would represent a change in the study conclusions. Clinical justification will be provided to evaluate whether the assumption is plausible.

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

DSN for each induction cycle will be presented using descriptive statistics. The primary analysis on DSN defined by Strategy 1 (refer to Section 6.2.7.1.1) will be repeated on DSN defined by Strategy 3 (refer to Section 5.1.1.2.3).

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

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

In addition to the summary from Kaplan-Meier method, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the stratification factors. The hazard ratio (HR) between the two treatments (trilaciclib vs placebo), together with its 95% CIs will be calculated from a Cox proportional hazard model in which treatment and the stratification factors 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.

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

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

6.2.7.2 Supportive Secondary Efficacy Analyses

6.2.7.2.1 Analyses of Total Number of MAHE

The total number of MAHE in Section 5.1.3.1 will be analyzed to compare trilaciclib and placebo using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. The logarithm transformation of duration of induction treatment period divided by 7 (i.e. week) will be included as an offset variable in the modeling. The two-sided p-value, aRR (trilaciclib vs placebo) and its 95% CIs will be presented.

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

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

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

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

6.2.7.2.2 Analyses of Objective Response

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

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

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

The binary endpoint (Yes, No) of ORR for the two treatments (trilaciclib and placebo) will be analyzed to compare trilaciclib and placebo using stratum-adjusted method to account for the stratification factors. The adjusted proportion difference (trilaciclib vs placebo) and its 95% CIs will be calculated using CMH weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method.

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

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

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

6.2.7.2.3 Analyses of DOR and PFS

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

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

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

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

6.2.7.2.4 Analyses of Hematology Lab Values

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

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

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

6.2.7.2.5 Analyses of Other Binary Efficacy Endpoints

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

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

[redacted]

6.2.8. Safety Analyses

All safety analyses will be based on the safety analysis set, as defined in Section 3.1.3. 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 applicable treatment period), and end of study (the last non-missing assessment during the whole study), if applicable. No inferential analyses of safety data are planned unless otherwise specified.

6.2.8.1. Chemotherapy Exposure and Compliance Analyses

Duration on treatment and number of cycles will be summarized by treatment. Dose modifications will be summarized for each study drug (trilaciclib, carboplatin, etoposide, or atezolizumab). For each study drug, the dosing endpoints described in Section 5.2.1 will be summarized for the induction treatment period. Atezolizumab specifics summaries will be summarized by maintenance and overall treatment periods as well. This includes the following:

- Number of cycles received;

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

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

6.2.8.2. Adverse Events

Number and incidence rates of AEs will be summarized by SOC and/or PT for the following categories of TEAEs: all AEs, SAEs, atezolizumab AESIs, 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 and SAEs will be summarized for the induction, maintenance, and overall treatment periods, the rest will be summarized for the overall treatment period only.

AEs will also be summarized similarly by CTCAE grade and relationship to any study drug (trilaciclib, carboplatin, etoposide, or atezolizumab), and by relationship to each drug. Should a patient experience more than one occurrence of the same SOC (PT), the patient's worst occurrence (worst grade/most related causality) will be retained in the tabulation. Those related to any study drug or atezolizumab will be summarized for the induction, maintenance, and overall treatment periods, the rest will be summarized for the overall treatment period only.

All AEs, including AEs that started prior to the study medication, will be presented in patient listings. In addition, separate listings of all SAEs, atezolizumab AESIs, AEs leading to death, drug-related AEs, and AEs leading to study drug discontinuation or study withdrawal will be provided.

The criteria for identifying infusion related reaction AEs or hematologic toxicity AEs are described in Section 5.2.2. A summary table showing the incidence of each category of AEs related to infusion and related to hematologic toxicity will be presented along with its supportive data listing. These will be summarized for the overall treatment period only.

6.2.8.3. Laboratory Evaluations

For hematology and clinical chemistry labs, the observed values and change from baseline will be summarized by cycle visit 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 overall 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 with normal reference ranges, and CTCAE grades (when possible) will be provided.

6.2.8.4. Vital Signs

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

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 14) during the overall treatment period will be presented. A listing of all vital sign data will be provided.

6.2.8.5. Performance Status

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

6.2.8.6. Physical Examination

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

6.2.8.7. ECG

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

The criteria for potentially clinically significant findings are defined in Table 16. The frequency and percentage of patients with any potentially clinically significant findings during the induction treatment period will be presented. The supportive data will be provided in patient data listings.

6.2.9. Subgroup Analyses

The MAHE will be examined in the following subgroups:

- Age group (ages <65; >65).
- Gender (Male; Female).
- Brain metastases (Yes; No).
- ECOG performance status (0-1; 2).
- Race (Caucasian; non-Caucasian).
- Region (US; Ex-US).
- Baseline LDH (≤ ULN; > ULN).

Descriptive statistics by treatment group will be presented for each subgroup of patients. Additional subgroups or endpoints may be identified and explored.

6.2.10. Pharmacokinetic Analysis

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

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

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

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

[redacted]

6.2.13. Planned Analysis

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

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

7. CHANGE FROM THE PROTOCOL

The endpoints and analyses listed below are based on the Statistics Section in the Protocol Amendment 2, dated 14 September 2018. The list displays the changes from the initial analysis indicated in the protocol.

8. REFERENCES

Brechenmacher T, Xu J, Dmitrienko A, Tamhane AC. A mixture gatekeeping procedure based on the Hommel test for clinical trial applications. *Journal of biopharmaceutical statistics*. 2011; 21: 748-767.

Dmitrienko A, Wiens BL, Tamhane AC, Wang X. Tree-structured gatekeeping tests in clinical trials with hierarchically ordered multiple objectives. *Statistics in medicine*. 2007; 26: 2465-2478.

Dmitrienko A, Tamhane, AC, Wiens B. General multistage gatekeeping procedures. *Biometrical Journal*. 2008; 50, 667-677.

Dmitrienko A, Tamhane, AC, Bretz F. *Multiple testing problems in pharmaceutical statistics*. 2009. Chapman and Hall/CRC.

Dmitrienko A, Tamhane AC. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. *Statistics in Medicine*. 2011; 30, 1473-1488.

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.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. (2012). https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man_en-0.pdf. Accessed 19 October 2018.

FDA Center for Biologics Evaluation and Research (CBER). Multiple Endpoints in Clinical Trials Guidance for Industry. https://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm536750.pdf. Published January 2017. Accessed 13 September 2018.

Huque MF. Validity of the Hochberg procedure revisited for clinical trial applications. *Statistics in medicine*. 2016; 35:5-20.

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

Yan X, Lee, S and Li N. Missing data handling methods in medical device clinical trials, *Journal of Biopharmaceutical Statistics*, 2009, 19 (6): 1085 — 1098

Zou G. A modified Poisson regression approach to prospective studies with binary data. *American journal of epidemiology*. 2004;159(7):702-6.

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; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 – 12.5 mg/dL; >2.9 – 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L	Corrected serum calcium of >12.5 – 13.5 mg/dL; >3.1 – 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L	-
Calcium (Hypocalcemia)	Corrected serum calcium of <LLN – 8.0 mg/dL; <LLN – 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 – 7.0 mg/dL; <2.0 – 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L	Corrected serum calcium of <7.0 – 6.0 mg/dL; <1.75 – 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 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	-

Table A-1 Clinical Laboratory Parameters CTCAE Criteria

Parameter	Grade				
	1	2	3	4	5
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	-	-
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Potassium (Hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	-
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	-
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
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.