STATISTICAL ANALYSIS PLAN

Protocol Title:	**PRESERVE 3: A Phase 2, Randomized, Open-Label Study of Trilaciclib Administered with First-Line Platinum-Based Chemotherapy and Avelumab Maintenance Therapy in Patients with Untreated, Locally Advanced or Metastatic Urothelial Carcinoma**
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Compound:	Trilaciclib for Injection, 300 mg/vial
Study Phase:	Phase 2
Study Name:	PRESERVE 3
Sponsor:	G1 Therapeutics, Inc.
Legal Registered Address:	700 Park Offices Dr. Suite 200 PO Box 110341 Research Triangle Park, NC 27709
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SAP SIGNATURE PAGE

I have read and understand the contents of this Statistical Analysis Plan, Version 2.0 for Study G1T28-209 dated 06 March 2024 and I agree with all the statistical approaches, variable derivations and data presentation detailed as described in this document.

06-Mar-2024

Date

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LIST OF ABBREVIATIONS

Abbreviation	Term
aCSR	Abbreviated CSR
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
aRR	Adjusted relative risk
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BOR	Best overall response
BPM	Beats per minute
BUN	Blood urea nitrogen
CDK	Cyclin dependent kinase
CI	Confidence interval
CIM	Chemotherapy-induced myelosuppression
CMH	Cochran–Mantel–Haenszel
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DCO	Data cutoff
DCR	Disease control rate
DMC	Data Monitoring Committee
DOR	Duration of response
DSN	Duration of severe neutropenia
ECG	Electrocardiogram

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ESA	Erythropoiesis-stimulating agent
ETV	End of Treatment Visit
FN	Febrile neutropenia
G-CSF	Granulocyte colony stimulating factor
Hgb	Hemoglobin
HR	Hazard ratio
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Wed Response System
LDH	Lactate dehydrogenase
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PCS	Potentially clinically significant
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic(s)
pMMR/MSS	Proficient mismatch repair/microsatellite stable
PR	Partial response
PT	Preferred term
RBC	Red blood cell
RE	Response evaluable
RECIST	Response Evaluable Criteria in Solid Tumors
SACT	Subsequent anticancer treatment

Abbreviation	Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCLC	Small cell lung cancer
SD	Stable disease
SE	Standard error
SI	Standard international
SN	Severe neutropenia
SOC	System organ class
SPSD	Statistical Programming Supportive Documents
TLF	Tables, listings, and figures
TOC	Table of contents
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides the detailed statistical methods, variable definitions and derivations, and data handling that will be applied to analyze clinical trial data (except pharmacokinetics [PK] data) collected from Study G1T28-209, "PRESERVE 3: A Phase 2, Randomized, Open-Label Study of Trilaciclib Administered with First-Line Platinum-Based Chemotherapy and Avelumab Maintenance Therapy in Patients with Untreated, Locally Advanced or Metastatic Urothelial Carcinoma" protocol version 3.0.

If there are differences between the statistical analysis approaches described in the SAP and those in the protocol, the methods and approaches in the SAP will supersede those in the protocol.

Statistical Programming Supportive Documents (SPSD) will be developed based on the SAP to serve as companion documents of the SAP to guide programming realization of the SAP. SPSD contain three separate documents: the table of contents (TOC) for planned analyses (in Excel Spreadsheet), reporting conventions (in Word), and shells or specificities for tables, listings, and figures (TLFs) generation (in Word).

Statistical software SAS® (SAS Institute Inc., Cary, NC) Version 9.4 or later will be used to perform data analyses following the plan as laid out in this SAP.

Changes and additions to the last signed off version of the SAP will be documented with corresponding rationale in the clinical study report (CSR).

The SAP for PK and PK/Pharmacodynamics analyses for Study G1T28-209 will be written as a separate document.

1.1. Study Design

This is an exploratory Phase 2, multicenter, randomized, open-label study evaluating the safety and efficacy of trilaciclib administered with platinum-based chemotherapy followed by trilaciclib administered with avelumab maintenance therapy compared with platinum-based chemotherapy followed by avelumab maintenance therapy in patients receiving first-line treatment for advanced/metastatic urothelial carcinoma.

Patients will be randomly assigned (1:1) to receive one of the following two treatment arms:

- Arm A – platinum-based chemotherapy followed by avelumab maintenance therapy (hereafter abbreviated as platinum/avelumab)
- Arm B – trilaciclib plus platinum-based chemotherapy followed by trilaciclib plus avelumab maintenance therapy (hereafter abbreviated as trilaciclib + platinum/avelumab)

There will be two stratification factors for randomization: presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin).

Study drugs will be administered as follows:

- Gemcitabine 1000 mg/m^2 administered IV on Day 1 and Day 8 of each 21-day chemotherapy cycle.
- Cisplatin eligible: cisplatin 70 mg/m^2 administered IV on Day 1 of each 21-day chemotherapy cycle. Split dosing on Day 1 and Day 8 is permitted for toxicity management as described in Protocol Section 9.3.1.1. Gemcitabine should be administered prior to cisplatin.
- Cisplatin ineligible: carboplatin using Calvert formula with a target area under the curve (AUC) = 4.5 administered IV on Day 1 of each 21-day chemotherapy cycle. Gemcitabine should be administered prior to carboplatin.
- Avelumab 800 mg administered IV on Day 1 of each 14-day maintenance cycle as a 60-minute infusion. To mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory for the first 4 infusions (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.
- Trilaciclib 240 mg/m^2 administered as a 30-minute IV infusion completed within 4 hours prior to the start of platinum-based chemotherapy (Day 1 and Day 8) at each cycle in chemotherapy period or avelumab maintenance therapy (Day 1) at each cycle in maintenance period.

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase (Figure 1: G1T28-209 Study Design Diagram). Patients enrolled in the study will be eligible to receive 4-6 cycles of platinum-based chemotherapy. The choice of either Cisplatin or Carboplatin will be determined by the Investigator. Patients will be allowed to switch from cisplatin to carboplatin chemotherapy if they become ineligible for cisplatin due to toxicity, or from carboplatin to cisplatin chemotherapy if they become eligible to receive cisplatin. Changes in protocol chemotherapy will not be allowed for the reason of suspected or confirmed disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

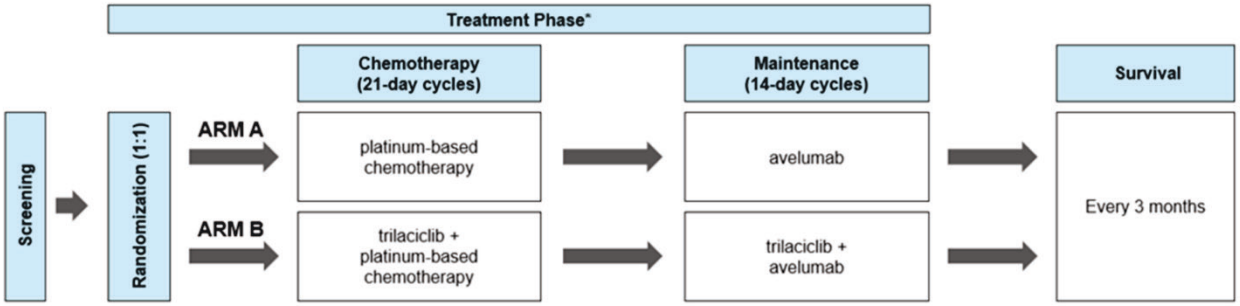
Patients without progressive disease (PD) per RECIST v1.1 after platinum-based chemotherapy will be eligible to receive avelumab maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first.

Upon discontinuation of study treatment, patients will be followed for survival until at least 60% of patients in the study have died, or the end of study, whichever occurs first.

A Data Monitoring Committee (DMC) will monitor accumulating safety and one-time anti-tumor response data as defined in the DMC charter.

The general design of the study, including study drugs administration in chemotherapy and maintenance periods, is depicted in the design diagram below.

Figure 1: G1T28-209 Study Design Diagram



* Randomized patients may receive 4-6 cycles of platinum-based chemotherapy (gemcitabine + cisplatin or gemcitabine + carboplatin) and patients without progressive disease per RECIST v1.1 (i.e., with ongoing CR, PR, or SD) after platinum-based chemotherapy may receive avelumab maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever occurs first.

1.2. Study Objectives

Primary:

To evaluate the anti-tumor efficacy of trilaciclib as compared to a control group.

Specifically, the primary and secondary objectives and their associated endpoints are described in Table 1.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To evaluate the anti-tumor efficacy of trilaciclib compared to a control group	• Progression-free survival (PFS) during the study
Secondary Objectives: Efficacy	
• To evaluate the anti-tumor efficacy of trilaciclib compared to a control group	• ORR (chemotherapy period, maintenance period, during the study) • DCR (maintenance period, during the study) • DOR (maintenance period, during the study) • PFS (maintenance period) • OS (maintenance period, during the study)
Secondary Objectives: Myeloprotection (to evaluate the myeloprotective effects of trilaciclib when combined with platinum-based chemotherapy compared with chemotherapy alone)	
• To assess the effects of trilaciclib on the neutrophil lineage compared to a control group during chemotherapy period	• Duration of severe (Grade 4) neutropenia in Cycle 1 • Occurrence of severe (Grade 4) neutropenia • Occurrence of febrile neutropenia AEs • Occurrence of G-CSF administration

Objectives	Endpoints
• To assess the effects of trilaciclib on the RBC lineage compared to a control group during chemotherapy period	• Occurrence of Grade 3 or 4 decreased hemoglobin laboratory values • RBC transfusions on or after Week 5 (occurrence and number of transfusions) • Occurrence of ESA administration
• To assess the effects of trilaciclib on the platelet lineage compared to a control group during chemotherapy period	• Occurrence of Grade 3 or 4 decreased platelet count laboratory values • Platelet transfusions (occurrence and number of transfusions)
• To assess the effects of trilaciclib on chemotherapy administrations compared to a control group during chemotherapy period	• All-cause dose reductions (occurrence and number of reductions) • All-cause cycle delays (occurrence and number of delays)
Secondary Objectives: Safety	
• To assess the safety and tolerability of trilaciclib compared to a control group	• Occurrence and severity of AEs by NCI-CTCAE v5.0 during chemotherapy and maintenance period • Trilaciclib AESIs during chemotherapy and maintenance period • Avelumab AESIs during maintenance period • Changes in laboratory parameters (hematology and serum chemistry), vital signs and ECG parameters during chemotherapy and maintenance period • Grade 3 or 4 abnormalities in serum chemistry laboratory parameters during chemotherapy and maintenance period • Occurrence of trilaciclib dose delays and infusion interruptions during chemotherapy and maintenance period • Occurrence of chemotherapy dose reductions during chemotherapy period • Occurrence of chemotherapy dose delays and infusion interruptions during chemotherapy period • Occurrence of avelumab dose delays and infusion interruptions during maintenance period

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; DCR=disease control rate; DOR=duration of response; ECG=electrocardiogram; ESA=erythropoiesis stimulating agent; G-CSF=granulocyte colony-stimulating factor; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RBC=red blood cell.

Other objectives and endpoints can be found in Section 8 and Section 9 of the protocol.

1.3. Sample Size Consideration

The sample size is calculated to support the primary objective of the study, that is, to evaluate trilaciclib's effect on PFS in patients who receive platinum-based chemotherapy followed by avelumab therapy as first-line treatment. From the literature, patients with urothelial carcinoma receiving avelumab maintenance therapy after platinum-based chemotherapy had a median PFS duration of 3.7 months (Powles, 2020). Considering 4 months chemotherapy prior to maintenance therapy in this study, the median PFS duration for the control group (Arm A): platinum-based chemotherapy followed by avelumab maintenance therapy) in this study is assumed to be 7 months.

A total of 63 PFS events will be required to achieve 77% power to detect a hazard ratio (HR) of 0.6 in PFS at a 2-sided significance of 0.2. An HR of 0.6 corresponds to a median PFS duration of 11.7 months for trilaciclib arm. Assuming 10 months of enrollment period and final PFS analysis taking place at approximately 22 months after the first patient is randomized, a total of 90 patients are required to be randomized at a 1:1 ratio to the control group (Arm A) or trilaciclib group (Arm B). In the sample size calculation, it is also assumed that about 5% of patients are lost-to-follow-up during the 22 months (equivalent to a monthly lost-to-follow-up rate of 0.0023315 assuming an exponential distribution). EAST® v6.5 is used for the power and sample size calculations.

2. THE NUMBER OF PLANNED ANALYSES

2.1. First Planned Analysis – Analyses for Objective Response Rate in the Chemotherapy Period, and Myelosuppression Endpoints

The first planned analysis will be conducted when all randomized patients have either completed at least 4 cycles of chemotherapy or discontinued during the chemotherapy period. The primary purpose of conducting the first planned analysis is to evaluate trilaciclib's effect on myelosuppression endpoints. It is believed that 4 cycles of chemotherapy exposure should be sufficient to perform the evaluation. Trilaciclib's effect on ORR will be evaluated in this analysis. Tumor assessment collected as of the data cutoff (DCO) date for this analysis will be included. As 4 cycles allow post-baseline tumor assessments, patients who achieved complete response (CR) or partial response (PR) from the first assessment will have the chance to be confirmed on the second assessment.

In addition, trilaciclib's safety in this patient population will be evaluated in this analysis.

There is no plan to lock the database to perform the analysis. Instead, a data snapshot will be taken at the time of a pre-specified DCO date following G1's Standard Operating Procedure for data snapshot to support the analyses planned at this time.

2.2. Intermediate Planned Analysis for Progression-Free Survival

The intermediate planned analysis will evaluate the effect of trilaciclib on PFS (the primary endpoint). The analysis for PFS, including subgroup analyses specified in Section 8.4.1, will be conducted at the time when 63 patients have radiographic determined disease progression or died.

In addition to the analysis of PFS, the following analyses may be conducted at the time when the intermediate planned analysis takes place:

- Overall Survival. Analysis of overall survival during the study, and selected overall survival analyses by subgroup as specified in Section 8.4.1.
- Myelosuppression Endpoints. Select myelosuppression endpoints specified in Table 9.

Similar to the first planned analysis, there is no plan to lock the database and a data snapshot will be taken to support these analyses.

Due to study termination prior to reaching the specified condition for conducting probability of survival at Month 16, the analysis for probability of survival at Month 16 will not be performed (see Section 2.4 and Section 10).

2.3. Final Analysis – Analysis for Overall Survival

The timing for the final analysis of OS was initially planned when approximately 60% randomized patients have died (i.e., 54 deaths). Due to study termination prior to reaching the specified number of deaths (see Section 2.4), the timing of final analysis is no longer contingent upon the number of deaths and will occur shortly after database lock (DBL). In addition to final

analysis of OS, the following analyses will be conducted, which represent a subset of analyses initially planned for the final analysis (see Section 2.4 and Section 10) according to the protocol:

- Analysis of tumor response endpoints (ORR, DCR, and DOR) during the study on the pooled data from both the chemotherapy and maintenance periods.
- Analysis of safety data from the maintenance period.

2.4. Change of Scope for Intermediate Planned and Final Analyses

The study was terminated early due to the changing landscape of bladder cancer treatment. Termination was not related to any safety issue. The last patient was dosed on 30NOV2023. An abbreviated CSR (aCSR) will be prepared in place of a full CSR after completion of final analysis. As a result, the following planned analyses from the intermediate planned analyses and final analysis will not be conducted:

- Intermediate planned analyses:
    - Probability of survival at Month 16.
- Final analysis:
    - Analysis of tumor response endpoints (ORR and DCR) during the maintenance period.
    - Analysis of anti-tumor endpoints during the overall study by CDK4/6 biomarker signature status and by PD-L1 subgroup.

3. ANALYSIS POPULATIONS

3.1. The Intent-to-treat Population

The Intent-to-treat (ITT) Population includes all randomized patients. Analyses for the ITT population will be conducted based on the randomly assigned treatment regardless of whether the patient received any study treatment or was compliant with the protocol. Unless otherwise specified, the ITT population is the primary population for all efficacy analyses.

3.2. The Response Evaluable Population

The Response Evaluable (RE) population includes those patients who are in the ITT population and receive at least one dose of any study drug, have measurable (target) tumor lesion(s) at baseline tumor assessment, and have at least one of the following: (1) at least 1 post-baseline tumor assessment; (2) discontinued treatment because of clinical progression prior to their first post-baseline tumor scan; (3) died due to disease progression prior to their first post-baseline tumor scan. Analyses using the RE population will be conducted on the basis of the randomly assigned treatment. It will be the primary analysis population for efficacy endpoints evaluating tumor responses.

3.3. The Safety Population

The Safety Population includes all randomized patients who received at least one dose of any study drug. Analyses using the safety population will be conducted on the basis of the actual treatment received at Day 1 of Cycle 1 in chemotherapy period. Unless otherwise specified, all safety data analyses for the chemotherapy period and overall treatment period will be performed based on this population.

3.4. The Maintenance Population

The Maintenance Population includes all randomized patients who received at least one dose of any study drug during the maintenance period. Unless otherwise specified, all analyses using this population will be based on the treatment group as initially assigned at randomization. That is, in Arm A (Chemotherapy/Avelumab) or Arm B (Trilaciclib + Chemotherapy/Avelumab).

4. GENERAL CONSIDERATIONS FOR DATA SUMMARY AND DISPLAY

4.1. Treatment Group Descriptions and Display in Table, Listings and Figures

As described in Section 1.1, eligible patients will be randomized at a 1:1 ratio to the treatment group of Chemotherapy/Avelumab or Trilaciclib + Chemotherapy/Avelumab. Depending on the type of platinum chemotherapies, each treatment group is further divided into Cisplatin-based or Carboplatin-based.

Patients enrolled in the study will be eligible to receive 4-6 cycles of platinum-based chemotherapy, per Investigator's discretion. Patients without progressive disease (PD) per RECIST v1.1 after platinum-based chemotherapy will be eligible to receive avelumab maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first.

Avelumab maintenance therapy (with or without trilaciclib) should begin at a minimum of 4 and not more than 10 weeks after the last dose of platinum-based chemotherapy (with or without trilaciclib).

An overview of treatment group descriptions by treatment phase that will be used in the SAP and TLFs with their corresponding descriptions in the protocol is provided in Table 2: Descriptions of Treatment Groups in Protocol, SAP, and Their Orders of Appearance in Table/Listing/Figures. In addition, the order by which the treatment groups will be displayed in TLFs is also provided in the table.

Table 2: Descriptions of Treatment Groups in Protocol, SAP, and Their Orders of Appearance in Table/Listing/Figures

Data included in the Analysis	Description in protocol	Description in SAP	Description in TLF	Order in TLF Display	
				Safety	Others
Chemotherapy Period	Platinum-based chemotherapy (Gemcitabine/Cisplatin or Gemcitabine/Carboplatin)	Chemo	Chemo	5	1
	Gemcitabine/Cisplatin	Gemcitabine/Cisplatin	Gem + Cis	1	
	Gemcitabine/Carboplatin	Gemcitabine/Carboplatin	Gem + Carbo	3	
	Trilaciclib + Platinum-based chemotherapy	Trilaciclib + Chemo	Trila + Chemo	6	2
	Trilaciclib + Gemcitabine/Cisplatin	Trilaciclib + Gemcitabine/ Cisplatin	Trila + Gem + Cis	2	
	Trilaciclib + Gemcitabine/Carboplatin	Trilaciclib + Gemcitabine/ Carboplatin	Trila + Gem + Carbo	4	
Maintenance Period	Avelumab	Avelumab	Avelumab	1	
	Trilaciclib + Avelumab	Trilaciclib/ Avelumab	Trilaciclib/ Avelumab	2	
Overall Treatment Period (Chemotherapy and Maintenance) OR During the study	Platinum-based chemotherapy followed by avelumab maintenance therapy (Arm A)	Chemo/Avelumab	Chemo/Avelumab	1	
	Trilaciclib plus platinum-based chemotherapy followed by trilaciclib plus avelumab maintenance therapy (Arm B)	Trilaciclib + Chemo/Avelumab	Trilaciclib + Chemo/Avelumab	2	

Cisplatin-based chemotherapy = Gemcitabine + cisplatin; Carboplatin-based chemotherapy = Gemcitabine + carboplatin; Platinum-based chemotherapy is either cisplatin-based chemotherapy or carboplatin-based chemotherapy. Carbo = carboplatin; Chemo = chemotherapy (Gemcitabine/Cisplatin or Gemcitabine/Carboplatin); Cis = cisplatin; Gem = gemcitabine; Trila = trilaciclib

4.2. Data Summary and Precision

General Principles of Data Summary

Data will be summarized by treatment group in table format. Tables summarizing disposition, demographics and baseline disease characteristics will include an overall column for patients pooled from all treatment groups. In general, continuous variables will be summarized descriptively, i.e., the following summary statistics will be presented:

- Number of patients with non-missing data (indicated by n)
- Mean and standard deviation
- Median
- Q1 (first quartile) and Q3 (third quartile)
- Minimum and maximum values.

Categorical variables will be summarized categorically, i.e., number (n) and percentage of patients in each category will be presented.

General Principles of Data Listings

All collected data and derived variables will be included in patient data listings. An indicator will be provided for any imputed data element (e.g., imputed adverse event [AE] start date). Columns in listings will be ordered by treatment group, country, study site, patient identification, visit, and assessment or event date, if applicable, and then the data elements. The treatment group presented in listings will be based on the randomly assigned treatment, unless otherwise noted.

General Principles of Precision for Summary Statistics and Calculated Statistical Quantities

The precision of summary statistics for continuous variables, including mean, median, Q1, Q3, minimum, and maximum, will be consistent with the precision of the variable as collected. Calculated quantities of variability (e.g., standard deviation, standard error [SE]) will be presented with one more decimal place than the precision of the variable that is collected. The boundaries of a confidence interval (CI) will keep the same precision as the point estimate.

For whole numbers (including counting variables), the mean, median, Q1, and Q3 will be presented with one decimal place.

For percentages, 1 digit will be presented after the decimal point (e.g., 10.1%). A percentage value less than 0.1% will be displayed as "<0.1%." A percentage value that is >99.9% and <100% will be displayed as ">99.9%."

P-values, in general, will be displayed in 3 decimal places except for when a p-value is <0.001, it will be presented as "<0.001". If a p-value is greater than 0.999, it will be displayed as ">0.999".

Rounding will take place after all calculation steps are completed prior to result display.

4.3. Definitions for Analysis Related Timepoint and Time Interval

Efficacy and safety data collected from this study will be summarized by chemotherapy period, maintenance period, during the overall treatment period (including chemotherapy and maintenance periods), or during the study (i.e., regardless of whether the patient was in chemotherapy, maintenance or survival follow-up period), depending on the category of the data to be summarized. For each specific category of data, the time interval by which the data will be analyzed or summarized will be specified in the respective section in which the data analysis plan is described.

The maximum duration for chemotherapy period is 6 cycles, which is equal to 18 weeks (126 days) under the assumption that there are no cycle delays or treatment interruptions.

To clarify data inclusion for each time interval of interest and baseline or end values for each given time interval, Table 3 presents definitions for timepoints, timepoint related assessments, and time intervals involved in statistical data analysis or summary.

Table 3: Definitions for Timepoints, Timepoint Related Assessments and Time Intervals

Term	Definition
Start of study (date)	Date of randomization
Study baseline (assessment)	The last non-missing value prior to or on the date of the first dose of any study drug at the time that is before the time of the first study drug administration.
Day 1 of Cycle X (date)	The date when the first dose of any study drug for Cycle X is administered.
End of cycle (date)	Day 1 of the subsequent cycle if there is a subsequent cycle, allowing crossing from chemotherapy period to maintenance period. For two special cases, 1) for the last Chemotherapy cycle and the patient did not enter maintenance and 2) the last maintenance cycle, the End of cycle is defined as the date of the End of Treatment Visit (ETV). If the ETV does not occur for a patient, the End of cycle for the patient will be defined as 14 days post the last dose of any study drugs in the respective cycle.
Duration of a cycle (days)	Total number of days from Day 1 of the cycle to End of the cycle, that is, End of the cycle – Day 1 of the cycle + 1.
Duration of study drug exposure in chemotherapy period (weeks)	Total number of weeks from Day 1 of Cycle 1 in chemotherapy period to the End of last chemotherapy cycle. That is, (End of last chemotherapy cycle – Day 1 of chemotherapy Cycle 1 + 1)/7.
Duration of study drug exposure in maintenance period (weeks)	Total number of weeks from Day 1 of Cycle 1 in maintenance period to the End of last maintenance cycle. That is, (End of last maintenance cycle – Day 1 of maintenance cycle 1 + 1)/7.
Duration of overall study drug exposure (weeks)	The total number of weeks from Day 1 of Cycle 1 in chemotherapy period to the End of the last cycle in the study (could be in chemotherapy or maintenance period). That is, (End of the last cycle in the study – Day 1 of chemotherapy Cycle 1 + 1) / 7.

Term	Definition
Duration of total follow-up (months)	The total number of months from date of randomization to either the date of death or last contact date in the study known alive. That is, duration of total follow-up = (date of death or date of last contact date known alive – date of randomization + 1) /30.4375.

4.4. Study Day

Study Day will be calculated for an event date or an assessment date to provide additional information for interpretation of the event occurrence. Study Day is calculated as:

- The start date of the event (visit date, onset date of an event, assessment date etc.) − the date of randomization + 1, if the event occurred on or after the reference date. Date of randomization will be Study Day 1.
- The start date of the event (visit date, onset date of an event, assessment date etc.) − the date of randomization, if the event occurred prior to the reference date. The day before the date of randomization will be Study Day -1.

4.5. General Principles of Missing Data Handling

For primary and secondary efficacy endpoints, handling of missing data is described in Section 8.3.

For all other data analyses, in general, the observed data are used for analyses or data summary. That is, no missing imputation will be performed. However, imputation of missing start or stop dates for AE and medications/therapies will be used to determine the status of each AE and the prior/concomitant/subsequent status of each non-study treatment medication/treatment. Please refer to Section 9.2.2 for the rules of imputation of missing AE start or stop date and Section 5.4 for the rules of imputation of missing medication start or stop dates.

For demographic and baseline characteristics, continuous variables will be summarized based on non-missing observations with the number of patients with non-missing data indicated. For a categorical variable with missing data, a category of “Missing” will be included as a separate category for the summary. That is, the number and percentage of patients in each category of the variable (including “Missing”) will be summarized and reported with the number of randomized patients as the denominator for the percentage calculation.

5. DISPOSITION AND BASELINE CHARACTERISTICS

5.1. Patient Disposition

A summary of patient disposition will be generated for each planned analysis using all accumulated data as of the data cutoff date for the respective analysis that will be conducted.

Patient disposition summary will include the following 4 major sections:

1. Disposition of all screened patients who signed informed consent
2. Study drug disposition for patients who received at least one dose of any study drug
3. Study disposition for patients who were randomized
4. Deaths among patients who were randomized

For Categories 2 and 3, the contents to be summarized and reported differ slightly among the planned analyses. Therefore, details are provided for each planned analysis. Specific details for each section are described below.

1. Disposition of all screened patients

The total number of screened patients who signed informed consent will be presented as two mutually exclusive groups: those who were screen failures and those who were randomized. For those who were randomized, patients who received at least one dose of any study drug and those who did not receive any dose of any study drug are further presented by treatment group and overall. The number of randomized patients will be the denominator for calculating percentages in each treatment group and overall.

2. Study drug disposition

A summary of study drug disposition will be generated for each planned analysis using all accumulated data as of the data cutoff date for the respective analysis that will be conducted.

For each study drug prescribed in chemotherapy period (trilaciclib, gemcitabine, cisplatin, and carboplatin), the number and percentage of patients who discontinued the study drug will be summarized by treatment group. Dispositions of cisplatin and carboplatin will be summarized for the patients who were treated at chemotherapy Cycle 1 Day 1 by the specific chemotherapy. In addition, the number and percentage of patients who have switched from cisplatin to carboplatin chemotherapy or from carboplatin to cisplatin chemotherapy will be summarized, with percentages calculated based on the number of patients who received the cisplatin and carboplatin chemotherapy at the start of chemotherapy, respectively.

For trilaciclib, the number and percentage of patients who continued with the study drug at maintenance Cycle 1 will also be summarized by treatment group. The number of patients who took trilaciclib at chemotherapy Cycle 1 will be the denominator for the percentage calculation.

For trilaciclib and avelumab during maintenance period, the number and percentage of patients who discontinued each study drug will be summarized by treatment group. The number of patients in the Maintenance population will be the denominator for the percentage calculation in each treatment group. Primary reasons for study drug discontinuation during maintenance period will be presented with the number and percentage of patients in each reason category, with

percentages calculated based on the number of patients who discontinued the study drug during maintenance period.

3. Study disposition

Disposition of Chemotherapy period

Out of those who entered chemotherapy period (i.e., who were randomized and had at least one dose of any study drug in chemotherapy period, the same as the Safety population), the number and percentage of patients in the following mutually exclusive categories will be summarized by treatment group and overall:

- Patients who are ongoing with chemotherapy
- Patients who have entered maintenance after chemotherapy
- Patients who have entered Survival follow-up without entering maintenance
- Patients who have discontinued from the study during chemotherapy period

The number of patients in the Safety population in each treatment group and overall will be the denominator for calculating percentages of patients in each of the categories.

Disposition of Maintenance period

Out of those in the maintenance population, the number and percentage of patients in the following mutually exclusive categories will be summarized by treatment group and overall:

- Patients who are ongoing with the treatment in maintenance period
- Patients who have entered Survival follow-up
- Patients who have discontinued from the study during maintenance period

The number of patients in the Maintenance population in each treatment group and overall will be the denominator for calculating percentages of patients in each of the categories.

Reason for Study Discontinuation

The primary reason for study discontinuation will also be summarized by treatment group and overall, and the number of patients who discontinued in the respective treatment group will be the denominator for the percentage calculation for each reason of discontinuation.

4. Death

The number and percentage of patients who died during the chemotherapy period, during the maintenance period, or during the study will be summarized by treatment group and overall for all randomized patients along with the primary reason of death (Progressive Disease, Adverse Event, Other). For calculating percentages of death, the number of randomized patients will be the denominator for during the chemotherapy period and during the study, and the number of patients in the maintenance period will be the denominator for during the maintenance period. The number of patients who died will be the denominator for calculating the percentage of patients within each primary reason for death.

Study drug and study disposition information will be provided in data listings for all randomized patients.

5.2. Demographics and Baseline Disease Characteristics

Demographics and baseline disease characteristics will be summarized for the first planned and final analyses.

Demographics will be summarized descriptively by treatment group and overall on the ITT population. Demographics include age (at screening), age group (≥18 to <65, or ≥ 65), gender, race, ethnicity, and country.

Baseline disease characteristics will also be summarized descriptively by treatment group and overall on the ITT population. Baseline disease characteristics include:

- Stage at initial diagnosis
- Stage at screening
- Site of the primary tumor
- Disease status
- Eastern Cooperative Oncology Group (ECOG) status
- Prior systemic therapy in adjuvant/neo-adjuvant setting
- Visceral metastasis (yes or no)
- Initial platinum-based chemotherapy administered (cisplatin or carboplatin)

All these baseline disease characteristics are categorical.

Data listings for demographics and baseline disease characteristics for the ITT population will be produced, respectively.

5.3. Medical History and Ongoing Conditions

Medical history and ongoing conditions at the Screening Visit will be summarized for the ITT population at the first planned and final analyses.

Non-cancer medical history and ongoing medical conditions collected at the Screening Visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or later, and then summarized by treatment group and overall for the ITT population. Medical history and ongoing conditions will be presented by system organ class (SOC) and preferred term (PT), with SOC and PT all sorted in descending frequency based on the overall column. A patient will only be counted once within a particular SOC (or PT) even if the patient had multiple conditions/diseases in the same SOC (or PT).

In addition, a data listing for medical history and ongoing medical conditions collected at the Screening Visit will be provided.

5.4. Prior and Concomitant Medications

Summaries of concomitant medications will be generated for the ITT population for the first planned and final analyses. Concomitant medications will be summarized for chemotherapy and maintenance period, separately.

Concomitant medications during chemotherapy period are those medications that were given during the time interval from the first dose of any study drug to the end of last chemotherapy cycle for patients who entered maintenance period. Concomitant medications during chemotherapy period for patients that did not enter the maintenance period are those medications that were given during the time interval from the first dose of any study drug to the last dose date of any study drug + 30 days. Concomitant medications during maintenance period are those medications that were given during the time interval from the first dose of any maintenance study drug to the last dose date during maintenance period + 90 days. Medications collected through electronic case report forms (eCRFs) will be coded to Anatomical Therapeutic Classification (ATC) and PT, where applicable, using the most recent World Health Organization Drug Dictionary (WHO-DD) version WHODrug-Global-B3 202309.

Prior and concomitant medications will be summarized by ATC classifications and PT and presented in a descending order of frequency for ATC and PT within an ATC based on the overall group. Terms at the lowest available level (Level 5 excluded) will be used for the ATC classifications. If a patient took multiple medications within the same ATC, the patient will only be counted once for that ATC. Similar logic applies to PT summaries. The number and percentage of patients receiving any prior/concomitant medications will be summarized by treatment group and overall.

Handling of Missing Start and/or End Date for Medications Entered into EDC

Medications with incomplete start and/or end dates will be imputed according to the specifications described below. Those with incomplete start and/or end dates will be assumed to be concomitant if it cannot be shown that the medication was not taken outside the treatment period.

For completely missing or partially missing start dates:

- If the start date has month and year but day is missing, the first dose date will be used if the month and year is the same as the first dose date, otherwise, the first day of the month will be used.
- If the start date has year, but day and month are missing, then the first dose date will be used if the year is the same as the first dose date, otherwise January 1st will be used.
- If the start date is completely missing, then it will be imputed as the first dose date of study drug.

After the imputation, the imputed start date will be compared with corresponding stop date, if available. If the imputed start date is later than the stop date, the start date will be imputed with the stop date instead.

For completely missing or partially missing stop dates:

- If the stop date has month and year but day is missing, the last day of the month will be used.
- If the stop date has year, but day and month are missing, December 31st will be used.

- If the stop date is completely missing, the last dose date will be used.

After the imputation, the imputed stop date will be compared against the death date for patients who died. If the date is later than the death date, the date of death will be used to impute the stop date instead.

Prior and concomitant medications will be listed with a flag for prior or concomitant.

5.5. Summary of Protocol Deviations

5.5.1. Definitions and Process for Identifying Protocol Deviations

A protocol deviation refers to situations where a patient's eligibility for study entry or a specific data collection deviate from the entry criteria or study procedure as specified in the protocol. Protocol deviation cases at the patient level with specific data elements of concern need to be summarized and reported in the aCSR. Protocol deviations will be categorized as major or minor. Major protocol deviations are those that could affect the integrity of the data or adversely affect patients' safety. Criteria that define major or minor protocol deviations will be specified, documented, and signed off on prior to study database lock. Specifically, a protocol deviation specifications document that describes the criteria defining major and minor protocol deviations, the categories of major protocol deviations, and the list of patients who had at least one protocol deviation case with the classification of major or minor will be created and signed off prior to study database lock to perform the unblinded statistical analysis.

The deviation of receiving a treatment that was not randomly assigned will be the only exception to the process described above. It will only be recognized after database lock. These cases will have an impact on the composition of the Safety population and a data listing for these patients will be included in the aCSR.

5.5.2. Summary of Protocol Deviations

A protocol deviation summary will be generated for the final analysis (including all protocol deviations occurring during and after chemotherapy period, separately).

The number and percentage of patients in the ITT population with protocol deviations will be tabulated for each of the following categories by treatment group and overall.

- Patients with at least one protocol deviation (major or minor)
- Patients with at least one major protocol deviation
- Patients with at least one protocol deviation in each of the major deviation categories

Protocol deviations will be listed with details and a flag for major or minor.

6. CLASSIFICATION OF PRIOR, CONCOMITANT, AND SUBSEQUENT ANTICANCER THERAPIES

Prior therapies refer to those anticancer treatments that patients received prior to first dose of any study drug, including medications, surgical procedures, or radiotherapy treatments.

Concomitant therapies refer to those treatments, other than study drugs, that could be utilized concurrently with study drug(s) as specified in the protocol. Equivalently, concomitant therapies include all non-study-treatment therapies that have started between the first dose date of any study drug and the last dose date of any study drug, inclusively.

Subsequent therapies refer to anticancer treatments received following investigational study drug discontinuation while the patient was still in the study (i.e., in the Survival Follow-up period).

The rules of imputation of missing start or stop dates for medications described in Section 5.4 are, in general, applicable for missing start or stop dates imputation for anticancer therapies in any format (medications, surgical procedures, or radiotherapy treatments).

6.1. Prior Anticancer Therapies

Summaries of prior anticancer therapies will be generated for the first planned analysis based on the ITT population.

The number and percentage of patients with any prior systemic anticancer treatments will be summarized by treatment group and overall. Prior anticancer medications will be further summarized based on ATC and PT and presented in a descending order of frequency for ATC and PT withing an ATC based on the overall group.

The number and percentage of patients with any prior surgical procedures that were related to bladder cancer and radiotherapies will be summarized by treatment group and overall, respectively.

6.2. Concomitant Anticancer Therapies

Summaries for concomitant anticancer therapies will be generated at the final analysis for the ITT population.

Concomitant anticancer therapies during chemotherapy period are defined as all anticancer therapies that start during the time interval from the first dose of any study drug to the end of last chemotherapy cycle for patients who entered maintenance period. Concomitant anticancer therapies during chemotherapy period for patients that did not enter the maintenance period are those medications that were given during the time interval from the first dose of any study drug to the last dose date of any study drug + 30 days. Concomitant anticancer therapies during maintenance period are those anticancer therapies that were given during the time interval from the first dose of any maintenance study drug to the last dose date during maintenance period + 90 days. The number and percentage of patients receiving any concomitant surgical procedures or radiotherapies will be summarized by treatment group and overall, respectively.

6.3. Subsequent Anticancer Treatments

Due to the early termination of the study (aCSR), subsequent anticancer treatments (SACTs) will not be summarized (see Section 2.4).

However, SACTs will be needed for the purpose of censoring in the programmatic derivation of parameters related to objective response rate (ORR), duration of objective response (DOR), and progression-free survival (PFS) (see Section 8.1.2.1.2).

Handling of Missing Start Date for SACTs Entered into EDC

SACTs with completely missing or partially missing start dates will be imputed according to the specifications described below.

- If the start date has month and year but day is missing, the date of discontinuation of last study drug will be used if the month and year is the same as the date of discontinuation of last study drug, otherwise, the first day of the month will be used.
- If the start date has year, but day and month are missing, then the date of discontinuation of last study drug will be used if the year is the same as the date of discontinuation of last study drug, otherwise January 1st will be used.
- If the start date is completely missing, then it will be imputed as the date of discontinuation of last study drug.

7. STUDY DRUG EXPOSURE AND MODIFICATION

7.1. Duration of Study Drug Exposure

Analyses described in this section will be based on the Safety population and will be performed at the first and final planned analyses unless otherwise specified.

7.1.1. Duration of Study Drug Exposure in Chemotherapy period

Duration of study drug exposure (weeks) in chemotherapy period is defined as the duration from Day 1 of Cycle 1 in chemotherapy period to the End of cycle for the last cycle in chemotherapy period. That is, duration of study drug exposure in chemotherapy period (weeks) = (End of cycle for the last chemotherapy cycle – Day 1 of chemotherapy Cycle 1 + 1)/7, where the definitions for End of cycle and Day 1 of Cycle 1 can be found in Section 4.3.

The duration of study drug exposure in chemotherapy period will be summarized by treatment group and overall. For each treatment group, the total number of cycles that a patient received will be summarized both categorically and descriptively.

Corresponding data listings will be provided.

7.1.2. Duration of Study Drug Exposure in Maintenance period and during the Study

Two additional variables will be calculated to report study drug exposure: the duration of study drug exposure in maintenance period and the duration of total study drug exposure (i.e., exposures from chemotherapy period and maintenance period combined). Specifically:

- Duration of study drug exposure in maintenance period (weeks) is defined as (End of cycle for the last maintenance cycle – Day 1 of maintenance Cycle 1 + 1)/7.
- Duration of total study drug exposure (chemotherapy and maintenance periods combined) (weeks) is defined as (End of cycle for the last cycle in the study – Day 1 of chemotherapy Cycle 1 + 1)/7.

The definitions for End of cycle and Day 1 of Cycle 1 can be found in Section 4.3.

Study drug exposure during the maintenance period will be summarized at the first planned, intermediate planned, and final analyses. For the patients in the Maintenance population, the duration of study drug exposure in maintenance period will be calculated and summarized by treatment group and overall. For each treatment group, the total number of maintenance cycles that a patient received will be summarized both categorically and descriptively.

Similarly, based on the Safety population, the duration of total study drug exposure will be summarized by treatment group and overall. For each treatment group, the total number of cycles that a patient received during the study will be summarized both categorically and descriptively. These analyses will only be performed at the final analysis.

Corresponding data listings will be provided.

7.2. Study Drug Modifications

Study drug modifications will be summarized at the first planned and final analyses unless otherwise specified.

There are three types of study drug modification: dose reduction, cycle delay, and infusion interruption. Protocol permitted dose reductions for each study drug are summarized in Table 4.

Table 4: Protocol Permitted Dose Reduction by Study Drug

Study Drug	Number of Dose Reductions Allowed
Trilaciclib	0
Gemcitabine	2
Cisplatin	2
Carboplatin	2
Avelumab	0

7.2.1. Chemotherapy Period

The number and percentage of patients will be summarized by treatment group based on the Safety population for each of the following categories:

1. Any study drug modification
2. Any dose reduction
3. Any cycle delay
4. Any cycle delay due to hematologic toxicity
5. Any infusion interruption

The number of any dose reduction and the number of any infusion interruption will be summarized descriptively and categorically by treatment group.

In addition, more detailed summaries outlined below will be provided.

Dose reduction for each chemotherapy. For each of the chemotherapies that dose can be reduced by protocol (in chemotherapy period: gemcitabine, cisplatin, and carboplatin), the number of dose reductions will be summarized descriptively and categorically by treatment group. The mutually exclusive categories are: Not Applicable (only one cycle), 0, 1, 2, and 3+. Reason for dose reduction will be summarized by treatment group.

Cycle delay. Information regarding whether a cycle was delayed was collected in the eCRF for each cycle. The number of cycles that have been delayed will be summarized descriptively and categorically by treatment group. The mutually exclusive categories are: Not Applicable (only one cycle), 0, 1, 2, and 3+. Reason for cycle delay will be summarized by treatment group.

Trilaciclib Infusion interruption. The number of trilaciclib infusion interruptions will be summarized descriptively and categorically by treatment group.

7.2.2. Maintenance Period

Study drug modifications during maintenance period will be summarized at the first planned, intermediate planned, and final analyses. The number and percentage of patients will be summarized by treatment group based on the Maintenance population for cycle delay and any infusion interruption.

The number of cycle delays and the number of any infusion interruption will be summarized descriptively and categorically by treatment group. Reason for cycle delays will be summarized by treatment group.

In addition, the number of trilaciclib infusion interruptions will be summarized descriptively and categorically by treatment group.

Corresponding data listings will be provided.

7.3. Duration of Total Follow-up

Duration of total follow-up will be summarized at the intermediate planned and final analyses.

Duration of total follow-up (months) refers to the time interval that a patient participated in this clinical study starting from the date of randomization. It will be calculated based on the definition provided below.

Duration of total follow-up (months) = (date of death or date of last contact date known as alive – date of randomization + 1) /30.4375.

The descriptive statistics for this variable will be included in the summary table for the OS analysis, and the patient level data will be included in the data listing described in Section 45.

8. EFFICACY ANALYSIS

Myelosuppression efficacy will be evaluated based on the data collected during chemotherapy period. Myelosuppression endpoints will be analyzed at the first planned analysis (see Section 2.1). Selected myelosuppression endpoints will be analyzed at intermediate and final planned analyses, unless otherwise specified.

Treatment effects on PFS and OS will be evaluated based on the estimated number of events and will not be limited by which study phase that the event was observed (e.g., in chemotherapy period, maintenance period, or survival follow-up period). When the number of events as specified in Sample Size Consideration (Section 1.3) are observed for PFS, data snapshot will be used to support the analyses of PFS and selected OS (see Section 15). Due to study termination prior to reaching the specified number of deaths (see Sections 2.3 and 2.4), the timing of final OS analysis is no longer contingent upon the number of deaths and will occur shortly after database lock (DBL).

8.1. Definitions of Efficacy Endpoints

8.1.1. Primary Efficacy Endpoint – Progression-Free Survival during the Study

Progressive disease (PD) and tumor response status are programmatically determined according to RECIST v1.1 based on the radiographic tumor measurements recorded on the eCRF by the Investigator for target lesions, the investigator assessment of non-target lesions, and the status of new lesions. For a patient, the status of PD will be determined using all radiographic tumor scan data assessed prior to or on the date of the data cutoff to conduct the analysis for PFS. In the situation where PD and withdrawal of consent, or PD and initiation of subsequent anticancer therapy, occurred on the same day for a patient, the PD status will be assumed for that patient. When applying RECIST v1.1, study baseline tumor assessment will be used.

PD and death due to any cause are referred to as PFS events. The PFS events during the study are cumulative and not limited to a specific treatment phase (chemotherapy, maintenance, or survival follow-up).

PFS is defined as the time (months) from date of randomization to the date of the first documented disease progression, or death in the absence of PD for those who had a PFS event, and the time from randomization to the censoring date for those who did not have a PFS event. Specifically, PFS is calculated as (date of PFS event or censoring – date of randomization + 1)/ 30.4375.

If a patient undergoes a palliative surgery/radiotherapy or a curative intent surgical procedure that impacts RECIST evaluation of one or more target lesions, then the patient will be censored on the last adequate radiologic assessment prior to the date of the surgery/radiotherapy.

Details for PFS calculation and censoring rules can be found in Table 5.

Table 5: Calculation of PFS during the Study and Censoring Rules

Situation	Date of Event or Censoring	Outcome
Disease progression per RECIST v1.1	Date of the first documented progression	PFS event

Death without a PD	Date of death	PFS event
Incomplete or no baseline tumor assessments	Date of randomization	Censored
Lacking information beyond randomization	Date of randomization	Censored
No progression	Date of the last adequate radiological tumor assessment with no documented disease progression	Censored
Subsequent anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment prior to the date of initiation of subsequent anticancer treatment	Censored
Palliative therapy started prior to documented disease progression	Date of last adequate radiologic assessment prior to the date of initiation of palliative therapy	Censored
Underwent curative intent surgical procedure	Date of last adequate radiologic assessment prior to the date of surgery	Censored

8.1.2. Secondary Efficacy Endpoints

8.1.2.1. Anti-tumor Efficacy Endpoints

8.1.2.1.1. Overall Survival during the Study

OS during the study is defined as the time (months) from the date of randomization to the date of death for patients who died in the study regardless of cause, or to the last contact date known to be alive for those who survived as of the date of data snapshot for intermediate planned analysis or final database lock for final analyses (censored cases). Patients lacking data beyond the date of randomization will have their survival time censored at the date of randomization. OS will not be censored even if a patient receives subsequent anticancer treatments.

8.1.2.1.2. Tumor Response and Duration of Objective Response

The following endpoints will be summarized for the chemotherapy, maintenance and survival follow-up periods, and the overall treatment period:

- Best overall response
- Objective response rate
- Duration of objective response (not applicable to chemotherapy period)
- Disease control rate

For derivation of these endpoints in the chemotherapy period, tumor scan data collected during chemotherapy period will be the basis to classify tumor response status for all patients in the RE population. For derivation of these endpoints in the maintenance and survival follow-up period, tumor scan data collected during maintenance period and survival follow-up periods will be the basis to classify tumor response status for patients in the Maintenance population. For derivation

of these endpoints in the overall treatment period, tumor scan data collected during chemotherapy, maintenance, and survival follow-up periods will be the basis to classify tumor response status for patients in the RE population.

If a patient has all or some of the following records prior to or on the DCO, the earliest date of those will be used to determine the inclusion of tumor scan data for response status derivation: (i) radiographic disease progression; (ii) withdrawal of consent to obtain scans; (iii) death; (iv) lost to follow-up; (v) initiation of palliative therapy; (vi) initiation of curative intent surgery; or (vii) initiation of subsequent anti-cancer therapy.

8.1.2.1.2.1. Tumor Response Status in Chemotherapy Period and in Overall Treatment Period

At each tumor assessment visit, an overall time point response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be determined programmatically using the measurements recorded on the eCRF by the Investigator for target lesions, the Investigator assessment of non-target lesions, and records of new lesions. When applying RECIST v1.1, the tumor assessment at Screening will be used as the baseline to derive tumor response status in the chemotherapy period and overall treatment period.

Best Overall Response

BOR categorizes a patient's tumor response status into one of following mutually exclusive categories per RECIST v1.1: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE). The minimum duration of stable disease must be 5 weeks starting from the date of randomization (the protocol scheduled tumor assessments is every 6 weeks ± 1 week in the chemotherapy period, every 8 weeks ± 1 week in the maintenance period for up to 1 year from Cycle 1 Day 1, and every 12 weeks ± 1 week thereafter).

Objective Response Rate

Achieving an objective response for a patient is defined as having a confirmed or unconfirmed CR or PR as the BOR. Objective response rate (ORR) is defined as the proportion of the patients who achieved objective response.

Confirmed Objective Response Rate

Confirmed CR or PR will be derived based on the principles described in RECIST v1.1. In the derivation, the minimum interval for confirmation of CR or PR is 4 weeks, and the minimum duration of treatment is 5 weeks (the protocol scheduled tumor assessments is every 6 weeks ± 1 week in the chemotherapy period). Confirmed ORR (confirmed CR or PR) is defined as the proportion of the patients who achieved confirmed objective response based on the RE population.

Duration of Objective Response (DOR)

Duration of Objective Response (DOR) in the overall treatment period is calculated for patients who achieved confirmed CR or confirmed PR as the BOR status. It is defined as the time (months) from the date when the objective response of CR or PR was first documented to the date that radiographic progressive disease is documented, or death, whichever comes first. That

is, DOR = (Date of documented disease progression or death – date of first documented confirmed CR or PR + 1)/30.4375. Patients who achieved SD, PD, or NE as the BOR status will be excluded from this analysis.

Censored DOR follows the same rules as the censoring rules for PFS (Table 5), except that the two scenarios of "Incomplete or no baseline tumor assessments" and "Lacking information beyond randomization" do not apply to DOR.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with BOR of confirmed CR, confirmed PR, or SD lasting at least 5 weeks.

8.1.2.1.2.2. Tumor Response Status in Maintenance and Survival Follow-up Periods

For the derivation of time point responses in the maintenance and survival follow-up periods, the last non-missing tumor assessment during chemotherapy period will be used as the baseline to derive tumor response status (hereafter referred to as maintenance baseline).

Patients who entered the maintenance period of the study (also defined as those patients in the Maintenance population) will be classified into three mutually exclusive groups based on their maintenance baseline tumor assessment status. For Group 1 and Group 2, timepoint tumor response status will be derived based on RECIST v1.1 principle with detailed rules as described in the following.

1. For patients with target lesion(s) at maintenance baseline (Group 1), Table 6 will be used for assessing time point response.
2. For patients with non-target lesion(s) only at maintenance baseline (Group 2), Table 7 will be used for assessing time point response.
3. For patients with neither target lesions nor non-target lesions (Group 3) at maintenance baseline, they will be reported as "No evidence of disease at maintenance baseline" in the summary of BOR.

Table 6: Time Point Response for Maintenance and Survival Follow-up Periods: Patients with Target Lesion(s) at Maintenance Baseline

Target Lesions Response	Non-Target Lesions		New Lesions	Overall Response
	Change from Maintenance baseline to Maintenance post-baseline	Response		
CR	Present → Absent*	CR	No	CR
CR	Present → Present	Non-CR/Non-PD	No	PR
CR	NE	NE	No	PR
PR	Present → Present	Non-CR/Non-PD/NE	No	PR
SD	Present → Present	Non-CR/Non-PD/NE	No	SD
NE	Present → Present	Non-PD	No	NE
PD	Any	Any	Yes or No	PD
Any	Absent → Present or Present → Unequivocal Progression	PD	Yes or No	PD
Any	Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable
* All non-target lesions need to be absent for a response of CR
For patients with target lesions and without any non-target lesion at maintenance baseline, if there is neither reappearance of any non-target lesion(s) nor any new lesion(s), overall response will be the same as response from target lesions.

Table 7: Time Point Response for Maintenance and Survival Follow-up Periods: Patients with Non-target Lesion(s) Only at Maintenance Baseline

Non-Target Lesions		New Lesions	Overall Response
Change from Maintenance baseline to Maintenance post-baseline	Response		
Present → Absent*	CR	No	CR
or Present → Present	Non-CR/Non-PD	No	Non-CR/Non-PD
Absent → Present or Present → Unequivocal Progression	PD	Yes or No	PD
Any	Any	Yes	PD
NE	NE	No	NE

CR = complete response, PD = progressive disease, and NE = not evaluable
* All non-target lesions need to be absent for a response of CR

Best Overall Response

The BOR status for patients in Group 1 is CR, PR, SD, PD, or NE. The minimum duration of stable disease must be 7 weeks starting from the first dose date of study drug in the maintenance period. The reason for using 7 weeks is that the protocol scheduled tumor assessments is every 8 weeks ± 1 week in the maintenance period for up to 1 year from Cycle 1 Day 1 and every 12 weeks ± 1 week thereafter. For patients in Group 2 the BOR status is CR, Non-CR/Non-PD, PD, or NE. Patients in the same BOR category (CR, PD, or NE) from Group 1 and Group 2 will be combined and summarized.

In summary, BOR in Maintenance and Survival Follow-up periods categorizes all patients who entered the Maintenance period into the following mutually exclusive categories: CR, PR, SD, Non-CR/Non-PD, PD, No evidence of disease at maintenance baseline, and NE.

Objective Response Rate

Achieving an objective response for a patient is defined as having a confirmed or unconfirmed CR or PR as the BOR. Objective response rate (ORR) is defined as the proportion of the patients who achieved objective response.

Confirmed Objective Response Rate

Confirmed CR or PR will be derived based on the principle described in RECIST v1.1. In the derivation, the minimum interval for confirmation of CR or PR is 4 weeks, and the minimum duration of maintenance treatment is 7 weeks (the protocol scheduled tumor assessments is every 8 weeks ± 1 week in the maintenance period for up to 1 year from Cycle 1 Day 1, and every 12 weeks ± 1 week thereafter). Confirmed ORR (confirmed CR or PR) is defined as the proportion of the patients who achieved confirmed objective response based on the Maintenance population.

Duration of Objective Response (DOR)

Duration of Objective Response (DOR) in the maintenance and survival follow-up periods is calculated for patients who achieved confirmed CR or confirmed PR as the BOR status in the maintenance and survival follow-up periods. It is defined as the time (months) from the date when the objective response of confirmed CR or PR was first documented to the date that radiographic progressive disease is documented, or death, whichever comes first. That is, DOR = (Date of documented disease progression or death – date of first documented CR or PR + 1)/30.4375. Only patients who achieved confirmed CR or confirmed PR as their BOR status in this reporting period will be included in this analysis.

Censored DOR follows the same rules as the censoring rules for PFS (Table 5), except that the two scenarios of “Incomplete or no baseline tumor assessments” and “Lacking information beyond randomization” do not apply to DOR.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with BOR of confirmed CR, confirmed PR, SD, or Non-CR/Non-PD.

8.1.2.1.3. Progression-free Survival and Overall Survival in the Maintenance and Survival Follow-up Periods

Both PFS and OS in the maintenance and survival follow-up periods are calculated for patients in the Maintenance population.

PD events in Groups 1 and 2 will be determined by rules specified in Table 6 and Table 7 in Section 8.1.2.1.2.2, respectively. For patients in Group 3, the appearance of any lesion(s) as recorded on either target lesion CRF, non-target lesion CRF, or new lesion CRF from any tumor assessments conducted in maintenance or survival follow-up period will be considered as a PD.

PFS in the maintenance and survival follow-up periods is defined as the time (months) from date of first dose of study drug in maintenance period to the date of the first documented disease progression or death in the absence of PD for those who had a PFS event during maintenance or survival follow-up period. For those who do not have any PFS event, PFS was censored. Specifically, PFS in the maintenance and survival follow-up periods is calculated as (date of PFS event or censoring – date of first dose of study drug in maintenance period + 1)/ 30.4375. Details for PFS calculation and censoring rules can be found in Table 8.

Table 8: Calculation of PFS in the Maintenance and Survival Follow-up Periods and Censoring Rules

Situation	Date of Event or Censoring	Outcome
Disease progression per RECIST v 1.1	Date of the first documented progression	PFS event
Death without a PD	Date of death	PFS event
Incomplete or no tumor assessments at maintenance baseline	Date of first dose of study drug in maintenance period	Censored
Lacking information beyond start of maintenance period	Date of first dose of study drug in maintenance period	Censored
No progression	Date of the last adequate radiological tumor assessment with no documented disease progression	Censored
Subsequent anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment prior to the date of initiation of subsequent anticancer treatment	Censored
Palliative therapy started prior to documented disease progression	Date of last adequate radiologic assessment prior to the date of initiation of palliative therapy	Censored
Underwent curative intent surgical procedure	Date of last adequate radiologic assessment prior to the date of surgery	Censored

OS in the maintenance and survival follow-up periods is defined as the time (months) from the date of first dose of study drug in maintenance period to the date of death for patients who died

in the Maintenance or Survival Follow up period regardless of cause, or to the last contact date known to be alive for those who survived as of the date for final database lock (censored cases).

8.1.2.2. Myelosuppression Efficacy Endpoints

Myelosuppression endpoints that are defined to assess trilaciclib's effect on multiple lineage protection in chemotherapy period are described in Table 9 by lineage (i.e., neutrophils, red blood cells [RBCs] and platelets). Endpoints that evaluate trilaciclib's impact on administration of current standard of care interventions to treat chemotherapy-induced myelosuppression (CIM), as well as to evaluate trilaciclib's impact on chemotherapy delivery in chemotherapy period and hospitalizations due to CIM are also described in Table 9.

All endpoints related to neutrophils, RBC, platelet, and lymphocyte will be derived from laboratory parameters. Unless otherwise specified, all endpoints described in Table 9 are derived based on data collected through scheduled and unscheduled visits during chemotherapy period.

Table 9: Myelosuppression Endpoints

Lineage	Endpoint	Type of Variable	Conducted in first planned analysis
Neutrophils	Duration of Severe Neutropenia in Cycle 1	Continuous	Yes
	Occurrence of severe neutropenia	Binary	Yes
	Number of cycles with severe neutropenia	Counting	Yes
	Occurrence of febrile neutropenia	Binary	Yes
	Occurrence of G-CSF administration	Binary	Yes
	Number of cycles with G-CSF administrations (event rate per 100 cycles)	Counting	Yes
	Occurrence of Grade 3 or 4 neutropenia	Binary	Yes
RBCs	Occurrence of Grade 3 or 4 decreased hemoglobin	Binary	Yes
	Occurrence of RBC transfusion on/after Week 5	Binary	Yes
	Number of RBC transfusions on/after Week 5 (event rate per 100 weeks)	Counting	Yes
	Occurrence of ESA administration	Binary	Yes
Platelets	Occurrence of Grade 3 or 4 decreased platelet counts	Binary	Yes
	Occurrence of platelet transfusion	Binary	Yes
	Number of platelet transfusions (event rate per 100 weeks)	Counting	Yes
Chemotherapy Modifications	Occurrence of chemotherapy dose reduction (all causes)	Binary	Yes
	Number of chemotherapy dose reductions (event rate per 100 cycles)	Counting	Yes
	Occurrence of cycle delay due to hematologic toxicity	Binary	Yes
	Number of cycle delays due to hematologic toxicity (event rate per 100 cycles)	Counting	Yes

ESA=erythropoiesis-stimulating agent; G-CSF=granulocyte colony stimulating factor; RBC=red blood cell; CIM= chemotherapy-induced myelosuppression

8.1.2.2.1.1. Neutrophil-Related Endpoints

Duration of Severe Neutropenia in Cycle 1

In Cycle 1, hematology laboratory parameters, including absolute neutrophil count (ANC), will be collected at Day 1 (prior to dosing), Days 1, 2, 8, 13, 17, and at the End of Cycle 1 (Day 1 pre-dose of Cycle 2) (See Table 3 in Section 4.3 for End of cycle definition). These ANC assessments along with unscheduled assessments obtained in Cycle 1, if they exist, will be used to calculate the DSN.

Severe neutropenia (SN) is defined as an ANC value $< 0.5 \times 10^9$/L (Grade 4 neutropenia per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] criteria, Version 5.0).

For patients with at least one SN event in Cycle 1, the following rules will be applied to calculate DSN (Days) in Cycle 1.

- For patients whose SN is resolved within Cycle 1 (defined as an ANC value $\geq 0.5 \times 10^9$/L at a date after the initial SN occurrence, and maintained until the end of Cycle 1), DSN in Cycle 1 will be derived as the number of days from the date of the first SN occurrence to the date of SN resolution.
- For patients who withdraw from the study during Cycle 1 with unresolved neutropenia, DSN in Cycle 1 will be derived as the total number of days from the date of the first SN occurrence to the date of withdrawal or the date of last contact in Cycle 1.

For patients without any SN in Cycle 1 or those who randomized but who did not receive any study drug, DSN will be set to 0. Actual ANC assessment dates rather than visit dates are used in the calculation of DSN in Cycle 1.

DSN is a continuous random variable but is not normally distributed given that a proportion of the values are set as 0 per definition described above.

Occurrence of Severe Neutropenia

Occurrence of SN during chemotherapy period (also referred to as occurrence of SN in the SAP) for a patient is defined as having as least one ANC value $< 0.5 \times 10^9$/L among all ANC measurements during chemotherapy period regardless of scheduled or unscheduled visits. Occurrence of SN is a binary random variable (Yes or No).

Number of Cycles with Severe Neutropenia

The number of cycles with SN in chemotherapy period for a patient is the total number of cycles in chemotherapy period where the patient had at least one SN event. For patients who did not have any SN event during chemotherapy period and those who were randomized but did not receive any study treatment, the value of 0 will be assigned. Number of cycles with SN is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

Occurrence of Febrile Neutropenia

Febrile neutropenia (FN) is an AE as reported by the Investigator and captured in the eCRF. A PT of FEBRILE NEUTROPENIA is used to identify a FN event. The occurrence of FN for a patient is defined as having at least one FN event in chemotherapy period and is a binary random variable (Yes or No).

Occurrence and Number of Granulocyte Colony Stimulating Factor (G-CSF) Administrations

Administration of G-CSF is collected throughout chemotherapy period. Cycles where G-CSF was administered will be identified by comparing the start and stop dates of each administration of G-CSF to cycle interval. If any of the time intervals in which G-CSF was administered overlapped with any dates between the start of a cycle and the end of the cycle, that cycle will be considered as having a G-CSF administration. Data handling conventions for missing start and stop dates are described in Section 5.4.

The occurrence of G-CSF administration during chemotherapy period for a patient is defined as having at least one cycle in which G-CSF was administrated for the patient during chemotherapy period. It is a binary random variable (Yes or No).

The number of cycles with G-CSF administrations in chemotherapy period for a patient is the total number cycles in chemotherapy period where the patient received at least one dose of G-CSF. If a dose of G-CSF was administrated on Day 1 of Cycle X (> 1), the following counting rules will apply:

- If the stop date was on Cycle X Day 1 and the start date was in the middle of Cycle X-1 or on Cycle X Day 1, an occurrence will be counted for Cycle X – 1 only. It was assumed that the triggering event has occurred in Cycle X-1.
- If the start date was on Cycle X Day 1 and stop date was in the middle of Cycle X, both Cycle X and Cycle X – 1 will be considered as having G-CSF administered. It was assumed that the triggering event has occurred in Cycle X-1, therefore, Cycle X-1 would be counted as an additional cycle in which G-CSF is administered.

For patients who did not have any G-CSF use during chemotherapy period and those who were randomized but did not receive any study treatment, the value of 0 will be assigned. Number of cycles with G-CSF administrations is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

Occurrence of Grade 3 or 4 Neutropenia

Occurrence of Grade 3 or 4 neutropenia during chemotherapy period for a patient is defined as having as least one ANC value $< 1.0 \times 10^9$/L among all ANC measurements during chemotherapy period regardless of scheduled or unscheduled visits. Occurrence of SN is a binary random variable (Yes or No).

8.1.2.2.1.2. RBC-Related Endpoints

Occurrence of Grade 3 or 4 Decreased Hemoglobin

Occurrence of Grade 3 or 4 decreased hemoglobin (Hgb) in chemotherapy period for a patient is defined as having at least one Hgb value that was < 8.0 g/dL among all scheduled or unscheduled assessments during chemotherapy period. It is a binary random variable (Yes or No).

Occurrence and Number of RBC Transfusion on/after Week 5

These two endpoints will be derived for those patients who had more than 4 weeks of study drug exposure during chemotherapy period.

Occurrence of RBC transfusions on/after Week 5 for a patient is defined as having at least one RBC transfusion on or after Week 5 (following Day 1 of Cycle 1) during chemotherapy period. Occurrence of RBC transfusions on/after Week 5 is a binary random variable (Yes or No).

The number of RBC transfusions on/after Week 5 for a patient is defined as the total number of RBC transfusions the patient had on/after Week 5 during chemotherapy period. Transfusions with a unique start date were counted as different events. For patients who did not have any RBC transfusion on/after Week 5 in chemotherapy period and those who were randomized but did not receive any study treatment, a value of 0 will be assigned. Number of RBC transfusions on/after Week 5 is a counting random variable and the summary statistics for this variable is event rate per 100 weeks.

Occurrence of Erythropoiesis-Stimulating Agent (ESA) Administration

Administration of ESA is collected throughout chemotherapy period. Cycles where ESA was administered will be identified by comparing the start and stop dates of each administration of ESA to cycle interval. If any of the time interval in which ESA was administered overlapped with any dates between the start of a cycle and the end of the cycle, that cycle will be considered as having an ESA administered. Data handling conventions for missing start and stop dates are described in Section 5.4.

The occurrence of ESA administration during chemotherapy period for a patient is defined as having at least one cycle in which ESA was administrated for the patient during chemotherapy period. It is a binary random variable (Yes or No).

8.1.2.2.1.3. Platelet-Related Endpoints

Occurrence of Grade 3 or 4 Decreased Platelet Counts

Occurrence of Grade 3 or 4 decreased platelet counts for a patient is defined as having at least one platelet count value that was $< 50.0 \times 10^9$/L among all scheduled or unscheduled assessments during chemotherapy period. Occurrence of Grade 3 or 4 decreased platelet counts is a binary random variable (Yes or No).

Occurrence and Number of Platelet Transfusions

Occurrence of platelet transfusion for a patient is defined as having at least one platelet transfusion during chemotherapy period. It is a binary random variable (Yes or No).

The number of platelet transfusions for a patient is defined as the total number of platelet transfusions the patient had during chemotherapy period. Transfusions with a unique start date during chemotherapy period were counted as different events. For patients who did not have any platelet transfusion in chemotherapy period and those who were randomized but did not receive any study treatment, the value of 0 will be assigned. Number of platelet transfusions is a counting random variable and the summary statistics for this variable is event rate per 100 weeks.

8.1.2.2.1.4. Chemotherapy Modifications

Occurrence and Number of Chemotherapy Dose Reduction

The occurrence of a chemotherapy dose reduction for a patient is defined as having at least one dose reduction in a cycle during chemotherapy period (regardless of which chemotherapy). Chemotherapies that allow dose reduction and the maximum number of reductions in chemotherapy period can be found in Section 7.2. Occurrence of chemotherapy dose reduction is a binary random variable (Yes or No).

Number of chemotherapy dose reductions for a patient is defined as the total number of chemotherapy dose reductions across 3 chemotherapies (Gemcitabine, Cisplatin, and Carboplatin), for which dose reduction was allowed per protocol during chemotherapy period. In addition, chemotherapy that was stopped due to toxicity will also be counted as one dose reduction event. The value of 0 will be assigned to those patients who did not have any chemotherapy dose reductions during chemotherapy period and those who were randomized but did not receive any study treatment. Number of chemotherapy dose reductions is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

Occurrence and Number of Cycle Delays Due to Hematologic Toxicity

Occurrence of cycle delays and the associated reason is collected in detail in the eCRF with the following mutually exclusive categories: low neutrophil count, low platelet count, both low neutrophil count and low platelet count, Other hematologic toxicity, Non-hematologic toxicity, or Other. A cycle delay is considered due to hematologic toxicity, if the associated reason is “low neutrophil count”, “low platelet count”, “both low neutrophil count and low platelet count”, or “Other hematologic toxicity”.

Occurrence of cycle delays due to hematologic toxicity for a patient is defined as having at least one cycle delay due to hematologic toxicity during chemotherapy period and is a binary random variable (Yes or No). The number of cycle delays due to hematologic toxicity for a patient is defined as the total number of cycles that were delayed due to hematologic toxicity for the patient during chemotherapy period. For patients who did not have any cycle delays due to hematologic toxicity in chemotherapy period and those who were randomized but did not receive any study treatment, the value of 0 will be assigned. Number of cycle delays due to hematologic toxicity is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

8.2. Statistical Analysis Methods

8.2.1. General Considerations for Efficacy Analysis

Unless otherwise specified, all efficacy analyses will be performed on the ITT population. Unless otherwise specified, the treatment effect on myelosuppression endpoints will be evaluated based on the data collected during chemotherapy period. Treatment effect on PFS and OS will be evaluated based on the number of events as stated in Section 1.3 and will not be limited to treatment phase (e.g., chemotherapy period, maintenance period, or Survival Follow-Up).

Stratification Factors and Factored to be Included in Statistical Models for Analysis

There will be two stratification factors for randomization: presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin). Presence of visceral metastasis will be abbreviated as "Visceral Metastasis" and initial platinum-based chemotherapy to be administered will be abbreviated as "Chemo Type" hereafter.

It is anticipated that both stratification factors will have an impact on patients' anti-tumor efficacy outcome, but only Chemo Type will have an impact on myelosuppression efficacy. Therefore, Chemo Type will be included as the factors in statistical analysis models evaluating trilaciclib's effect of myeloprotection, while both stratification factors will be included in the statistical analysis models to assess trilaciclib's anti-tumor efficacy. Unless otherwise specified, the strata information as entered in IWRS at the time of randomization will be used as the factors for all stratified statistical analyses.

Family-wise Type 1 Error Rate Control and Nominal P-values

As described in the protocol and further detailed in the sections below, the family-wise Type 1 error rate of 2-sided 0.2 is only applied for the primary endpoint. For secondary efficacy endpoints, nominal p-value and 95% CI will be generated as the reference for judging strength of the evidence and the precision of point estimation.

8.2.2. Analysis for Primary Efficacy Endpoint – Progression-Free Survival during the Study

8.2.2.1. Primary Analysis

The analysis for PFS during the study will be performed when 63 PFS events are obtained. It will also be conducted at the final analysis of the study.

For PFS, the number and percentage of patients with a PFS event (radiographic disease progression or died due to any cause) or censored will be summarized by treatment group along with the reasons for censoring. Furthermore, the number and percentage of patients with disease progression or who died due to any cause will be summarized by treatment group with the number of PFS events as the denominator for percentage calculation.

The treatment effect for PFS will be primarily evaluated using a stratified log-rank test accounting for the two stratification factors. The magnitude of treatment effect, HR (Arm B vs. Arm A) along with its 80% CI will be estimated using a Cox proportional hazard model controlling for the same factors as included in the stratified log-rank test.

For each treatment group, the Kaplan-Meier plots will be generated and the median, 25% and 75% percentile of PFS will be estimated using the Kaplan-Meier method with their corresponding 95% confidence interval calculated based on the method by Brookmeyer and Crowley (1982). Additionally, Kaplan-Meier estimates will be provided for the survival probability along with their 95% confidence intervals (Kalbfleisch, 1980) at selected landmarks of 12, 24, 36, and 48 months.

8.2.3. Analysis for Secondary Endpoint - Overall Survival during the Study

The analysis for OS during the study will be performed at two timepoints:

1. When the intermediate planned PFS analysis is conducted, i.e., when 63 PFS events have occurred.
2. At the final analysis when approximately 60% randomized patients have died (i.e., 54 deaths), which will trigger the lock of study database to perform all SAP specified analyses.

Due to study termination prior to reaching the specified number of deaths (see Sections 2.3 and 2.4), the timing of final OS analysis specified in point 2 above is no longer contingent upon the number of deaths and will occur shortly after database lock (DBL).

For OS, the number and percentage of patients who died or are censored will be summarized by treatment group. In addition, duration of total follow-up will also be summarized by treatment group.

The treatment effect for OS will be primarily evaluated using a stratified log-rank test accounting for the two stratification factors. The magnitude of treatment effect, HR (Arm B vs. Arm A) along with its 80% CI will be estimated using a Cox proportional hazard model controlling for the same factors as included in the stratified log-rank test.

For each treatment group, the Kaplan-Meier plots will be generated and the median, 25% and 75% percentile of OS will be estimated using the Kaplan-Meier method with their corresponding 95% confidence interval calculated based on the method by Brookmeyer and Crowley (1982). Additionally, Kaplan-Meier estimates will be provided for the survival probability along with their 95% confidence intervals (Kalbfleisch, 1980) at selected landmarks of 12, 16, 24, 36, and 48 months.

8.2.4. Analysis for Secondary Endpoints - Other Anti-tumor Efficacy Endpoints

The analysis for BOR, ORR, DCR, and DOR (see variable definitions in Section 8.1.2.1.2) for both chemotherapy period and overall treatment period will be based on the RE population. The analysis of these endpoints for maintenance and survival follow-up periods will be based on the Maintenance RE population and it will be conducted at following timepoints:

1. At the first planned analysis
2. At the time of PFS analysis

Tumor response status classified by BOR will be tabulated by treatment group with the number and percentage of patients in each response category, where the percentages are calculated based on the number of patients in the population for the respective period.

ORR and DCR, along with their exact 95% two-sided CIs using the Clopper-Pearson method will be computed for each treatment group. The treatment effect on ORR and DCR will be evaluated using a Cochran–Mantel–Haenszel (CMH) test accounting for the stratification factors. The adjusted proportion difference (Arm B vs. Arm A) and its 95% CI will be calculated using CMH weight (as described in Kim, 2013).

For patients who achieved confirmed CR or confirmed PR as BOR status, DOR will be analyzed. The Kaplan-Meier method will be used to estimate the median, 25% and 75% percentile of DOR

for each treatment group, along with its 95% CI calculated using the method by Brookmeyer and Crowley (1982).

8.2.5. Analysis for Secondary Endpoints – Progression-free Survival and Overall Survival in the Maintenance and Survival Follow-up Periods

Analysis of PFS in the maintenance and survival Follow-up periods and OS in the Maintenance Period will be performed at the final analysis.

PFS in the maintenance and survival follow-up periods will be analyzed using the same methods as used for the primary analysis of PFS during the study.

OS in the maintenance and survival follow-up periods will be analyzed using the same methods as used for the analysis of OS during the study.

8.2.6. Analysis for Secondary Endpoints - Myelosuppression Endpoints

Statistical analysis methods for myelosuppression endpoints derived based on data collected in chemotherapy period (Section **Error! Reference source not found.**) are described in this section. The analysis of myelosuppression endpoints will be based on the ITT population and performed for the first planned (see the selected list in Table 9), intermediate planned (selected endpoints), and final analyses (selected endpoints). Corresponding data listings will be provided.

8.2.6.1. Analysis for Duration of Severe Neutropenia

Treatment effect on DSN in Cycle 1 will be evaluated using nonparametric analysis of covariance (ANCOVA) (Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020;383(13):1218-30.

Quade 1967). In this analysis, the rank-transformed (within each stratum) DSN values will be analyzed by an ANCOVA model with the terms of treatment and Chemo Type. Rank-transformed baseline ANC (within each stratum) will be included as a covariate in the model. In addition, the group-difference in DSN in Cycle 1 (trilaciclib/SOC – SOC), its standard error and 95% CI will be generated and reported from a Satterthwaite t-test and presented.

8.2.6.2. Analysis for Binary Myelosuppression Endpoints

For each binary myelosuppression endpoint as specified in Table 9 in Section 8.1.2.1.2.1, the number and percentage of patients with at least one occurrence during chemotherapy period will be summarized by treatment group.

The treatment effect will be evaluated using a modified Poisson regression model (Zou, 2004). The model includes the factors of treatment and Chemo Type as the fixed effect and corresponding baseline value as a covariate when applicable. The variable duration of chemotherapy period among patients will be adjusted by using the log-transformed duration of chemotherapy period (in the unit of cycles or weeks) as the offset variable in the model. A 2-sided p-value, adjusted relative risk (aRR, Arm B vs. Arm A) and its 95% CI will be generated from the modified Poisson regression model and reported.

Baseline value to be used as a covariate in the model is determined by the lineage of the endpoint (Table 9 in Section 8.1.2.1.2.1) and they are paired in the following manner: baseline ANC for

neutrophil-related endpoints, baseline hemoglobin for RBC-related endpoints, and baseline platelet for platelet-related endpoints.

The duration of chemotherapy period that is used to construct an offset variable in the model is the number of cycles in chemotherapy period for all binary endpoints but two: occurrence of RBC transfusion on/after Week 5 and occurrence of platelet transfusion. For these two endpoints, the total number of weeks in chemotherapy period that is the same as the duration of study drug exposure in chemotherapy period (defined in Table 3, Section 4.3) will be used as the duration variable.

8.2.6.3. Analysis for Counting Myelosuppression Endpoints

For the counting myelosuppression endpoints as specified in Table 9 (Section 8.1.2.1.2.1), the total number of the events, the duration of chemotherapy period (in the unit of cycles or weeks), and raw event rate per 100 units (weeks or cycles) will be summarized by treatment group.

The treatment group difference in the event rate will be assessed by a negative binomial model. The model includes the treatment and Chemo Type as the fixed effect and corresponding baseline value as a covariate when applicable. The various duration among patients will be adjusted in assessing treatment effect by using the log-transformed duration of chemotherapy period as the offset variable in the model. A 2-sided p-value, aRR (Arm B vs. Arm A) and its 95% CI will be generated from the negative binomial model and reported.

Baseline value to be used as a covariate in the model is determined by the lineage of the endpoint (Table 9 in Section 8.1.2.1.2.1) and they are paired in the following manner: baseline ANC for neutrophil-related endpoint, baseline hemoglobin for RBC-related endpoints, and baseline platelet for platelet-related endpoints.

The duration of chemotherapy period (used to calculate the raw event rate and to construct an offset variable in the model) is the number of cycles in chemotherapy period for the endpoints of number of G-CSF administrations and number of dose reductions, and it is the number of weeks in chemotherapy period for the two other counting random variables: number of RBC transfusions on/after Week 5 and number of platelet transfusions. The total number of weeks in chemotherapy period is the same as the duration of study drug exposure in chemotherapy period, which is defined in Table 3 (Section 4.3).

8.3. Handling of Missing Data

Unless otherwise specified, all efficacy data will be evaluated as reported and no imputation of missing values will be done. Impact of missing data on efficacy endpoints are in general managed by derivation rules (Section 8.1).

8.4. Subgroup Analysis

Subgroup analysis for the primary efficacy endpoint PFS will be performed at the intermediate planned analysis for PFS.

8.4.1. Subgroup Analysis for PFS

The following subgroups have been identified to assess whether treatment effect on PFS is consistent for each of the identified subgroups.

1. Age group (< 65 or ≥ 65)
2. Gender (male or female)
3. Baseline ECOG Status (0 or 1)
4. Region (US, Western Europe, or Eastern Europe)
5. Visceral metastasis (yes or no)
6. Chemo Type (cisplatin or carboplatin)
7. PD-L1 status (positive or negative)

Within each stratum of Age group, Gender, and ECOG, a Cox proportional hazard model with the terms of treatment, Visceral metastasis, and Chemo Type will be used to estimate the HR (Arm B vs. Arm A) and its 95% CI for PFS. Treatment-by-subgroup interaction will be tested by a different Cox model based on the ITT population with additional terms of the subgroup and the treatment-by-subgroup interaction. Statistically significant interaction is judged by an interaction p-value that is < 0.25.

To generate HR and its 95% CI within each stratum for the subgroup that is used as the stratification factors, Visceral metastasis or Chemo Type, the same factor will be eliminated from the Cox model to estimate the HR and its 95% CI. Treatment-by-subgroup interaction for these subgroups will not be tested, since these two were chosen as randomization stratification factors because of the anticipated impact on the outcome of PFS.

9. SAFETY ANALYSIS

9.1. General Consideration of Safety Analysis

Safety data summaries will be based on the Safety Population as defined in Section 3.3 of this SAP. The main purpose of safety analysis is to assess the safety and tolerability of trilaciclib in patients receiving platinum-based chemotherapy followed by avelumab maintenance therapy. This can be broken down to evaluate the safety of trilaciclib when added on to chemotherapy and the safety of trilaciclib when added on to maintenance therapy of avelumab. The safety of trilaciclib when added on to chemotherapy can be further evaluated by the type of platinum used in chemotherapy: safety of trilaciclib when added on to cisplatin-based chemotherapy and safety of trilaciclib when added on to carboplatin-based chemotherapy.

Unless otherwise specified, safety data collected in chemotherapy period and maintenance period will be summarized separately. For the chemotherapy period, safety data will be tabulated for the comparison of the following treatment groups:

1. Trilaciclib + Chemo vs Chemo
2. Trilaciclib + Gemcitabine/Cisplatin vs Gemcitabine/Cisplatin
3. Trilaciclib + Gemcitabine/Carboplatin vs Gemcitabine/Carboplatin

For the maintenance period, safety data will be tabulated for the Avelumab and Trilaciclib + Avelumab treatment groups. The scheme of table layouts has been defined in Table 2:
Descriptions of Treatment Groups in Protocol, SAP, and Their Orders of Appearance in Table/Listing/Figures.

At the time of first planned and final analysis, all safety data collected during the study will be summarized. Safety variable definitions and the data analysis plan as described in this section will be applied to both analyses unless otherwise specified. As such, the phrase of “during the treatment period” refers to the respective analysis period of interest.

Safety data will be summarized using descriptive statistics by treatment group and for overall patients when appropriate. No inferential statistical comparisons for between-group differences will be made. All safety data collected through scheduled or non-scheduled visits from Day 1 of Cycle 1 to the safety follow-up visit will be included in the safety data analyses. Missing safety data will generally not be imputed, unless otherwise specified.

Baseline assessment is, in general, defined as the last non-missing observation prior to receiving the first dose of any study drug.

9.2. Adverse Events

9.2.1. Definition and Classification of Adverse Events

AEs are defined as those AEs occurring on or worsening in severity after the first dose of any study drug (i.e., the conventional treatment-emergent AEs). Only AEs as described above are collected in the study database. For patients not in the Maintenance population, all AEs will be reported since the first dose of any study drug until 30 days after the last dose of study drug and

they will be reported for the chemotherapy period and overall treatment period. For patients in the Maintenance population, all AEs will be reported for the overall treatment period since the first dose of any study drug until 90 days after the last dose date during maintenance period. All AEs that start from the first dose of any study drug to end of last chemotherapy cycle will be reported for the chemotherapy period. All AEs that start from the first dose of any maintenance study drug to the last dose date during maintenance period will be reported for the maintenance period. Serious adverse events (SAEs) thought to be related to a study specific procedure are also collected between the time the patient signs the informed consent and the first dose of any study drug.

AEs will be coded from verbatim text to PT and grouped by primary SOC according to MedDRA version 25.1 or higher. The severity (toxicity grades 1-5) of AEs will be graded according to the NCI CTCAE version 5.0 by the Investigator.

Trilaciclib Adverse Events of Special Interest

AEs of special interest (AESI) for trilaciclib have been identified, reflecting either the findings in the AEs from the previous studies of trilaciclib or class effects for CDK 4/6 inhibitors. AESI for trilaciclib will be identified by searching MedDRA PTs based on the Customized MedDRA Queries as detailed in Appendix 2.

Specifically, trilaciclib AESI include the following 5 categories:

- Injection site reaction/Phlebitis/Thrombophlebitis
- Acute drug hypersensitivity reaction
- Hepatotoxicity
- Interstitial lung disease/Pneumonitis
- Embolic and thrombotic events, venous

9.2.2. Imputation Rules for Missing Start or Stop Date for Adverse Events

AEs with start/stop dates that are partially or completely missing that are not ongoing at the time of data cutoff will be imputed according to the specifications below in order to classify AEs.

For completely missing or partially missing AE start date:

- If the start date has month and year but day is missing, the first dose date will be used if the month and year is the same as the first dose date, otherwise, the first day of the month will be used.
- If the start date has year, but day and month are missing, then the first dose date will be used if the year is the same as the first dose date, otherwise January 1st will be used.
- If the start date is completely missing, then it will be imputed as the first dose date of study drug.

After the imputation, the imputed start date will be compared with AE stop date, if available. If the imputed start date is later than the stop date, the start date will be imputed with the stop date instead.

For completely missing or partially missing AE stop dates:

- If the stop date has month and year but day is missing, the last day of the month will be used.
- If the stop date has year, but day and month are missing, December 31st will be used.
- If the stop date is completely missing, the date of ETV will be used; if ETV does not exist, then the last dose date + 30 days will be used.

After the imputation, the imputed AE stop date will be compared against the death date for patients who died. If the date is later than the death date, the date of death will be used to impute the stop date instead.

Every attempt will be made to obtain complete information for AEs regarding severity (i.e., CTCAE Grade) and relationship to drug. However, in the rare case of missing data, the following conservative approach will be taken for summary purpose. The non-imputed raw data will be presented in AE listings.

- Missing AE grade will be classified as "Grade 3"
- Missing AE relationship will be classified as "Related"

9.2.3. Analysis for Adverse Events

AEs will be summarized by number and percentage of patients having at least one occurrence at the PT and SOC level by treatment group and overall. Patients with more than one occurrence of the same SOC (PT) will be counted only once within the SOC (PT) categorization. In general, the percentage of patients with an event will be calculated using the number of patients in the safety population as the denominator either by each treatment group or overall.

AEs will also be summarized by CTCAE grade and relationship to study drug (to any study drugs and to each individual study drug). Should a patient experience more than one occurrence of the same SOC (PT), the patient's worst occurrence (highest grade or highest related causality) will be used for the analysis and reporting.

In AE summaries for chemotherapy period, the SOC and PT within a SOC will be presented in descending order based on the incidence from the Trilaciclib + Chemo column. In AE summaries for maintenance period, the SOC and PT within a SOC will be presented in descending order based on the incidence from the Trilaciclib + Avelumab column. If the incidence for two or more PTs is equal, these PTs will be presented in alphabetical order.

An overall AE summary table will be generated to present general information related to AEs including the following categories: number and percentage of patients with any AE, Serious AEs, AEs with CTCAE Grade ≥ 3 or 4, AEs leading to discontinuation of any study drug, AEs leading to death, AEs related to study drug (to any study drug, to trilaciclib, and to each other study drug), and AESI for trilaciclib.

At the time of performing final analysis, in addition to generating the overall AE summary table for the data collected during the chemotherapy and maintenance period, an overall AE summary table will also be generated for the AEs collected during the overall treatment period.

In addition, the following summary tables will be generated, and they will be, in general, presented by SOC and PT unless otherwise specified.

1. AEs by decreasing frequency of PT
2. AEs by SOC, PT, and CTCAE Grade
3. AEs with CTCAE Grade 3 or 4 by PT and CTCAE Grade
4. AEs leading to discontinuation of any study drug
5. AEs leading to discontinuation of trilaciclib
6. AEs leading to death
7. AEs related to any study drug
8. AEs related to trilaciclib
9. Serious AEs
10. Serious AEs related to any and each study drug
11. AESI for trilaciclib

Corresponding AE listings will be provided to clearly indicate, at the patient level, the AE and SAE occurrence, start/stop date, relative study days to start or stop, grade and causality for each AE. AESI for trilaciclib will also be listed with a similar level of detail.

9.3. Clinical Laboratory Data

9.3.1. Laboratory Parameters

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 10 will be measured according to Schedule of Assessments in Appendix 1.

Table 10: Laboratory Categories and Parameters

Lab Category	Lab Parameters
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, blood urea nitrogen (BUN)
Hematology	hemoglobin, white blood cell (WBC), platelet counts, absolute neutrophil count (ANC), absolute lymphocyte count (ALC)
Urinalysis	semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin microscopic examination, including

	red blood cell (RBC), white blood cell (WBC), and casts will be performed, if necessary

Lab = laboratory.

Lab data during chemotherapy period are those that were collected during the time interval from the first dose of any study drug to the end of last chemotherapy cycle for patients who entered maintenance period or last dose date of any study drug + 30 days for patients who did not. Lab data during maintenance period are those that were collected during the time interval from the first dose of any maintenance study drug to the last dose date during maintenance period + 30 days.

For hematology parameters, if absolute counts are not provided, those values will be derived from the differential counts by multiplying differential value with leukocyte value from the same sample. The normal ranges will be left missing in those cases.

Clinical chemistry and hematology assessments will be graded according to NCI CTCAE criteria, Version 5.0 or later. The determination of CTCAE grade for each measurement will be based on the collected laboratory values and will not involve clinical judgement. For laboratory parameters that CTCAE toxicity grade are not available, they will not be included in the analyses in which toxicity grades are reported. Instead, these parameter results will be classified and reported by the low/normal/high based on the laboratory normal reference ranges.

Abnormal Hepatic Laboratory Values

Abnormal hepatic laboratory values are defined in the following categories including any occurrence among all on-treatment, post-baseline assessments including scheduled and unscheduled values.

- Hy's Law:
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN), alkaline phosphatase (ALP) < 2xULN, and total bilirubin ≥ 2xULN
    - Pre-existing baseline ALT, AST, OR total bilirubin values are above the upper limit of normal, and the patient subsequently presents with:
        - AST or ALT ≥ 2 times the baseline value and ≥ 3x ULN, or ≥ 8x ULN (whichever is smaller)
        - **Concurrent** with total bilirubin ≥ 2 times the baseline value OR ≥ 3x ULN (whichever is smaller)
- AST: > 3 and ≤ 5x ULN, > 5 and ≤ 8x ULN, > 8 and ≤ 10x ULN, > 10 and ≤ 20x ULN, and > 20x ULN; AST > 5x ULN for more than 5 weeks.
- ALT: >3 and ≤ 5x ULN, > 5 and ≤ 8x ULN, > 8 and ≤ 10x ULN, > 10 and ≤ 20x ULN, and > 20x ULN; ALT > 5x ULN for more than 5 weeks.
- Total bilirubin > 1.5xULN and < 2xULN, ≥ 2xULN

9.3.2. Analysis for Laboratory Parameters

Laboratory data from all central and local laboratories will be included in analyses. Different laboratories are likely using slightly different normal reference ranges, which should not affect the planned analysis since they are all categorical and reported based on CTCAE toxicity grade or relationship to the normal ranges. The default convention for reporting of laboratory units will be standard international (SI) units. If a lab value is reported using an inequality symbol e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary. Data will be presented in listings with their inequality symbol.

For each lab parameter, baseline for the chemotherapy period is defined as the last non-missing value prior to, or on the first date of administration of any study drug(s) in the chemotherapy period; baseline for maintenance period is defined as the last non-missing value prior to, or on the first date of administration of any study drug(s) during maintenance period. In both scenarios, baseline assessment must be done prior to the time of study drug administration.

For each parameter in the clinical chemistry and hematology laboratory groups, CTCAE toxicity grading is used to classify patients into a toxicity grade from 1 to 4 for each timepoint assessment. The number and percentage of patients with highest grade during the treatment period will be summarized for each grade from 1 to 4 and Grade 3-4 by treatment group, along with such summary for the value collected at baseline.

For the laboratory parameters that cannot be classified by CTCAE grade, the number and percentage of patients in the categories of treatment-emergent low or treatment-emergent high based on the normal reference range associated with the parameter will be summarized by treatment group.

The number and percentage of patients in each category of abnormal hepatic laboratory values will be summarized by treatment group.

Laboratory parameters will be listed by the groups of chemistry, hematology, and urinalysis. In the data listing, flags that indicate the corresponding CTCAE grades and the classifications relative to the laboratory reference ranges will be included. In addition, a separate listing will be prepared for patients who met Hy's law.

9.4. Vital Signs

9.4.1. Vital Sign Parameters

Vital signs including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, and body temperature will be measured according to Schedule of Assessments in Appendix 1.

Vital signs during chemotherapy period are those that were collected during the time interval from the first dose of any study drug to the end of last chemotherapy cycle. Vital signs during maintenance period are those that were collected during the time interval from the first dose of any maintenance study drug to end of last maintenance cycle.

Baseline vital signs for the chemotherapy period is defined as the last non-missing value prior to, or on the first date of administration of any study drug(s) in the chemotherapy period; baseline

vital signs for maintenance period is defined as the last non-missing value prior to, or on the first date of administration of any study drug(s) during maintenance period. In both scenarios, baseline assessment must be done prior to the time of study drug administration.

Post-baseline assessments refer to the measurements taken after the first dose of any study drug and during treatment period. Change from baseline to the highest/lowest value across all post-baseline measurements for each vital sign parameter will be calculated. Patients with a non-missing baseline and at least one non-missing measurement post-first dose for a given parameter will be included in the calculation.

Patients are classified with respect to the criteria of potentially clinically significant (PCS) findings of vital signs, which are defined by the highest/lowest value among post-baseline assessments and/or the change from baseline to the highest/lowest observed value. Details of PCS criteria for vital signs can be found in Table 11.

Table 11: Criteria for Potentially Clinically Significant Vital Signs

Parameter	Direction	Highest/Lowest Observed Value	Change from Baseline to the Highest/Lowest Observed Value
SBP	High	≥ 180 mmHg	Increase ≥ 40 mmHg
	Low	≤ 90 mmHg	Decrease ≥ 40 mmHg
DBP	High	≥ 105 mmHg	Increase ≥ 20 mmHg
	Low	≤ 50 mmHg	Decrease ≥ 20 mmHg
Heart Rate	High	≥ 120 bpm	Increase ≥ 40 bpm
	Low	≤ 50 bpm	Decrease ≥ 40 bpm
Weight	High	--	Increase ≥ 10%
	Low	--	Decrease ≥ 10%

bpm=beats per minute; DBP=diastolic blood pressure; SBP=systolic blood pressure

9.4.2. Analysis for Vital Signs

Number and percentage of patients who meet any PCS criteria for each vital sign parameter as well as for each criterion will be summarized by treatment group.

All observed vital sign values and PCS flag will be listed.

9.5. ECOG Performance Status

ECOG performance status was assessed at the Screening Visit and at Day 1 of each treatment cycle during the study.

ECOG status during chemotherapy period are those that were collected during the time interval from the first dose of any study drug to the end of last chemotherapy cycle. ECOG status during

maintenance period are those that were collected during the time interval from the first dose of any maintenance study drug to end of last maintenance cycle.

Baseline ECOG for the chemotherapy period is defined as the last non-missing value prior to, or on the first date of administration of any study drug(s) in the chemotherapy period; baseline ECOG for maintenance period is defined as the last non-missing value prior to, or on the first date of administration of any study drug(s) during maintenance period. In both scenarios, baseline assessment must be done prior to the time of study drug administration.

9.6. 12-lead Electrocardiograms

As ECG is only collected at screening, no analysis will be planned.

10. CHANGES FROM THE PROTOCOL

- The protocol has defined the timing for the first planned analysis as "The first planned analysis will be conducted when all randomized patients have either completed chemotherapy or discontinued during the chemotherapy period". This has been changed to "The first planned analysis will be conducted when all randomized patients have either completed at least 4 cycles of chemotherapy or discontinued during the chemotherapy period". This is because the primary purpose of conducting the first planned analysis was to evaluate trilaciclib's effect on myelosuppression endpoints. It is believed that 4 cycles of chemotherapy exposure should be sufficient to perform the evaluation.
- The protocol listed "occurrence and number of hospitalizations due to chemotherapy-induced myelosuppression" as an endpoint to assess the effects of trilaciclib on hospitalizations due to chemotherapy-induced myelosuppression compared to a control group (Protocol Section 5 and Table 4). Due to the early termination of the study (aCSR), this endpoint will not be evaluated.
- The protocol has included the analysis of "Probability of survival at Month 16" as part of the intermediate planned analyses (Protocol Section 12.3.2). Due to the early termination of the study (aCSR), this analysis will not be conducted (See Section 2.2 and Section 2.4 for details).
- The protocol indicated that subsequent anticancer therapies (surgical procedure, radiotherapy, and systemic anticancer medication) for the ITT population will be summarized by treatment group and overall (Protocol Section 12.4.4). Due to the early termination of the study (aCSR), this summary is deemed non-critical and will not be provided (See Section 2.4 and Section 6.3).
- The protocol indicated that for trilaciclib, avelumab, gemcitabine, cisplatin/carboplatin, cumulative dose, dose intensity, relative dose, and relative dose intensity will be derived and summarized by treatment group (Protocol Section 12.4.5). Due to the early termination of the study (aCSR), this summary is deemed non-critical and will not be provided (See Section 2.4).
- To understand the effects of trilaciclib in CDK 4/6-dependent tumors when added to platinum-based chemotherapy and avelumab maintenance therapy, the protocol listed a summary of number and percentage of patients in different CDK 4/6 biomarker signature status (CDK 4/6 independent, CDK 4/6 dependent, and CDK 4/6 indeterminate) and the analysis of anti-tumor endpoints (PFS, ORR, and OS) during the overall study by CDK 4/6 signature status subgroup as an exploratory analysis at the time of final planned analysis (Protocol Section 12.4.8). Due to the early termination of the study (aCSR), these analyses will not be conducted.

11. REFERENCES

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12. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Study Treatment								Follow-Up		
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up
Assessment	**30 days prior to C1D1**	**Day 1 (±1d)**	**Day 2**	**Day 8 (±1d)**	**Day 13 and Day 17 (±1d)**	**Day 1 (±1d)**	**Day 2**	**14 days after last dose of study drug (±3d)**	**30 days after last dose of study drug (+7d)**	**90 days after last dose of avelumab (±7d)**	**Every 3 months after ETV (±7d) [a]**
Informed Consent	X										
Randomization		X [C1 only (-7d)]									
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical History and Surgical History	X										
Archival and/or fresh FFPE tumor specimen or 15 unstained slides	X										
Concomitant Medications	X	X		X		X		X	X	X	
Complete Physical Examination	X										
Physical Examination when symptoms warrant per Investigator discretion		X				X		X			

	Study Treatment								Follow-Up		
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up
Assessment	30 days prior to C1D1	Day 1 (±1d)	Day 2	Day 8 (±1d)	Day 13 and Day 17 (±1d)	Day 1 (±1d)	Day 2	14 days after last dose of study drug (±3d)	30 days after last dose of study drug (+7d)	90 days after last dose of avelumab (±7d)	Every 3 months after ETV (±7d) [a]
Vital Signs	X	X		X		X		X			
ECOG Performance Status	X	X				X [every-other cycle]		X			
AE Reporting		X									
Hematology	X	X	X [C1 only]	X	X [C1 only]	X		X	X		
Chemistry	X	X				X		X	X		
Free T4 and TSH	X					X [Q8 wk]		X			
Urinalysis (dipstick)	X							X			
Pregnancy Test (WOCBP only)	X	X				X [every-other cycle; C1 start]		X			
Anti-avelumab antibody and neutralizing antibody testing						X [C1, C3, C6 only]		X			

	Study Treatment								Follow-Up		
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up
Assessment	**30 days prior to C1D1**	**Day 1 (±1d)**	**Day 2**	**Day 8 (±1d)**	**Day 13 and Day 17 (±1d)**	**Day 1 (±1d)**	**Day 2**	**14 days after last dose of study drug (±3d)**	**30 days after last dose of study drug (+7d)**	**90 days after last dose of avelumab (±7d)**	**Every 3 months after ETV (±7d) [a]**
12-lead ECG	X										
Blood samples for biomarkers		X [C1, C2, C3 only]		X [C1 only]		X [C1, C3 only]					
Blood samples for trilaciclib and metabolites PK (Arm B only)		X [C1 only]	X [C1 only]			X [C1, C3, only]	X [C1, C3, only]				
Blood samples for cisplatin PK (only patients treated with cisplatin)		X [C1 only]		X [C1 only]							
Blood samples for avelumab PK (Arm B only)						X [C1, C3, C6 only]					
Trilaciclib (Arm B only)		X		X		X					
gemcitabine		X		X							
cisplatin [b] or carboplatin		X		X [b]							
avelumab						X					

	Study Treatment								Follow-Up		
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up
Assessment	**30 days prior to C1D1**	**Day 1 (±1d)**	**Day 2**	**Day 8 (±1d)**	**Day 13 and Day 17 (±1d)**	**Day 1 (±1d)**	**Day 2**	**14 days after last dose of study drug (±3d)**	**30 days after last dose of study drug (+7d)**	**90 days after last dose of avelumab (±7d)**	**Every 3 months after ETV (±7d) [a]**
Tumor Assessments (CT/MRI)	X	CT/MRI of chest/abdomen/pelvis Q6 weeks (±7d) during the chemotherapy period and Q8 weeks (±7d) during the avelumab maintenance period for up to 1 year relative to Cycle 1 Day 1 and Q12 weeks (±7d) thereafter relative to Cycle 1 Day 1 until documented disease progression or subsequent anticancer therapy. Brain scan (MRI preferred) during screening is not required and should be performed per investigator discretion based on clinical signs and symptoms. Additional brain MRI should be conducted if there are brain metastases present at baseline or new clinical signs and symptoms suggestive of brain metastases. Bone metastases identified at baseline via a bone scan or PET (such as FDG-PET, NaF-PET, or other locally available PET options) to be followed at scheduled visits using localized CT or MRI as clinically indicated. If bone metastases cannot be seen on CT or MRI scans, bone scans, or PET should be repeated, using the same diagnostic procedure bone metastases were at baseline, when CR is identified in target disease or when progression in bone is suspected.									
Survival Follow-Up and Subsequent Anti-Cancer Treatments [a]											X

AE=adverse event; C=cycle(s); CR=complete response; CT=computed tomography; d=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ETV=End of Treatment Visit; FDG=[^{18}F]-fluorodeoxyglucose; FFPE=formalin-fixed paraffin-embedded; MRI=magnetic resonance imaging; NaF=sodium fluoride; PET=positron emission tomography; PK=pharmacokinetic; Q6=every six; Q8=every 8; Q12=every 12; rand.=randomization; T4=thyroxine; TSH=thyroid stimulating hormone; wk=weeks; WOCBP=women of childbearing potential.

[a] Survival follow-up assessments should occur every 3 months after the End of Treatment Visit (including assessments at Month 17 Day 1 [±7d].

[b] Splitting the dose of cisplatin to Day 1 and Day 8 dosing is an allowed alternative for toxicity management (refer to Protocol Section 9.3.1.1).

APPENDIX 2. CUSTOMIZED MedDRA QUERIES FOR TRILACICLIB AESIs

AESI Categories	Preferred Terms	
Injection Site Reaction/ Phlebitis/ Thrombophlebitis	Administration site phlebitis Application site phlebitis Catheter site phlebitis Chemical phlebitis Infusion site phlebitis Infusion site thrombosis Injection site phlebitis Injection site thrombosis	Periphlebitis Phlebitis Phlebitis deep Phlebitis infective Septic phlebitis Thrombophlebitis Thrombophlebitis septic Thrombophlebitis superficial Vascular access site thrombosis
	Administration related reaction Administration site dermatitis Administration site hypersensitivity Administration site pain Administration site rash Administration site recall reaction Administration site urticaria Administration site vasculitis Application site dermatitis Application site hypersensitivity Application site pain Application site rash Application site recall reaction Application site urticaria Application site vasculitis Catheter site dermatitis Catheter site hypersensitivity Catheter site pain Catheter site rash Catheter site urticaria Catheter site vasculitis Immediate post-injection reaction Infusion-related reaction Infusion site dermatitis	Infusion site erythema Infusion site hypersensitivity Infusion site pain Infusion site rash Infusion site reaction Infusion site recall reaction Infusion site urticaria Infusion site vasculitis Injection related reaction Injection site dermatitis Injection site erythema Injection site hypersensitivity Injection site pain Injection site rash Injection site reaction Injection site recall reaction Injection site urticaria Injection site vasculitis Installation site urticaria instillation site hypersensitivity instillation site pain instillation site rash Skin reaction Vessel puncture site rash Vessel puncture site vesicles

AESI Categories	Preferred Terms	
Acute drug hypersensitivity reaction	Allergic bronchitis	Laryngitis allergic
	Allergic cough	Laryngospasm
	Allergic eosinophilia	Laryngotracheal oedema
	Allergic oedema	Lip edema
	Allergic pharyngitis	Lip swelling mast cell degranulation present
	Allergic reaction to excipient	Mouth swelling
	Allergic respiratory disease	Oedema mouth
	Allergic respiratory symptom	Oropharyngeal oedema
	Anaphylactic reaction	Oropharyngeal spasm
	Anaphylactic shock	Oropharyngeal swelling
	Anaphylactic transfusion reaction	Palatal oedema
	Anaphylactoid reaction	Palatal swelling
	Anaphylactoid shock	Periorbital oedema
	Anaphylaxis treatment	Periorbital swelling
	Angioedema	Pharyngeal oedema
	Bronchospasm	Pharyngeal swelling
	Circulatory collapse	Pruritus allergic
	Circumoral oedema	Reaction to excipient
	Circumoral swelling	Shock
	Distributive shock	Shock symptom
	Documented hypersensitivity to administered product	Swelling face
	Drug hypersensitivity	Swelling of eyelid
	Drug reaction with eosinophilia and systemic symptoms	Swollen tongue
	Epiglottic oedema	Therapeutic product cross-reactivity
	Eye oedema	Tongue oedema
	Eye swelling	Tracheal oedema
	Eyelid oedema	Type I hypersensitivity
	Face oedema	Urticaria
	Hypersensitivity	Urticaria contact
	Immune-mediated adverse reaction	Urticaria popular
	Infusion related hypersensitivity reaction	Urticarial dermatitis
	Laryngeal oedema	Urticarial vasculitis

AESI Categories	Preferred Terms	
Hepatotoxicity	Acute hepatic failure Acute on chronic liver failure Acute yellow liver atrophy Allergic hepatitis Autoimmune hepatitis Cholestatic liver injury Chronic hepatic failure Chronic hepatitis Coma hepatic Drug-Induced Liver Injury Hepatic failure Hepatic infiltration eosinophilia Hepatic necrosis Hepatic steato-fibrosis Hepatic steatosis Hepatitis	Hepatitis acute Hepatitis cholestatic Hepatitis chronic active Hepatitis chronic persistent Hepatitis fulminant Hepatitis toxic Hepatocellular foamy cell syndrome Hepatocellular injury Hepatotoxicity Immune-mediated hepatitis Liver disorder Liver injury Mixed liver injury Non-alcoholic steatohepatitis Steatohepatitis Subacute hepatic failure
Interstitial Lung Disease (ILD) /Pneumonitis	Acute interstitial pneumonitis Acute lung injury Acute respiratory distress syndrome Alveolar lung disease Alveolitis Alveolitis necrotizing Autoimmune lung disease Diffuse alveolar damage Eosinophilic pneumonia Eosinophilic pneumonia acute Eosinophilic pneumonia chronic Granulomatous pneumonitis Hypersensitivity pneumonitis	Idiopathic interstitial pneumonia Idiopathic pneumonia syndrome Idiopathic pulmonary fibrosis Immune-mediated pneumonitis Interstitial lung disease Necrotizing bronchiolitis Obliterative bronchiolitis Pneumonitis Pneumonitis chemical Progressive massive fibrosis Pulmonary fibrosis Pulmonary toxicity Restrictive pulmonary disease

AESI Categories	Preferred Terms	
Embolic and thrombotic events, venous	Axillary vein thrombosis	Pulmonary thrombosis
	Brachiocephalic vein occlusion	Pulmonary vein occlusion
	Brachiocephalic vein thrombosis	Pulmonary veno-occlusive disease
	Deep vein thrombosis	Pulmonary venous thrombosis
	Embolism venous	Subclavian vein occlusion
	Iliac vein occlusion	Subclavian vein thrombosis
	Obstructive shock	Superior vena cava occlusion
	Pelvic venous thrombosis	Thrombosis
	Peripheral vein occlusion	Vena cava embolism
	Peripheral vein thrombus extension	Vena cava thrombosis
	Phlebectomy	Venous occlusion
	Pulmonary embolism	Venous thrombosis
	Pulmonary microemboli	Venous thrombosis limb