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STATISTICAL ANALYSIS PLAN

Protocol Title:	**PRESERVE 1: A Phase 3 Randomized, Double-blind Trial of Trilaciclib versus Placebo in Patients Receiving FOLFOXIRI/Bevacizumab for Metastatic Colorectal Cancer**
Protocol Version	6.0
Protocol Number:	G1T28-207
Compound:	Trilaciclib for Injection, 300 mg/vial
Study Phase:	Phase 3
Study Name:	PRESERVE 1
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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Statistical Analysis Plan Version:	V 3.0
Document Completion:	19 Dec 2022
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SAP SIGNATURE PAGE

I have read and understand the contents of this Statistical Analysis Plan, Version 3.0 for Study G1T28-207 dated 09 January 2023 and I agree with all the statistical approaches, variable derivations and data presentation detailed as described in this document.

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Date

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LIST OF ABBREVIATIONS

Abbreviation	Term
5FU	Fluorouracil
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
aRR	Adjusted relative risk
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BOR	Best overall response
CBC	Complete blood count
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 cut-off
DOR	Duration of response
DSN	Duration of severe neutropenia
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ESA	Erythropoiesis-stimulating agent
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue

Abbreviation	Term
FACT-An	Functional Assessment of Cancer Therapy - Anemia
FDA	Food and Drug Administration
GCSF	Granulocyte colony stimulating factor
Hgb	Hemoglobin
HR	Hazard ratio
ICE	Intercurrent event
ICH	International Council for Harmonisation
ID	Identification
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Wed Response System
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PCS	Potentially clinically significant
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic(s)
pMMR/MSS	Proficient mismatch repair/microsatellite stable
PP	Per-protocol
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
PTV	Post Treatment Visit
RBC	Red blood cell
RE	Response evaluable
RECIST	Response Evaluable Criteria in Solid Tumors

Abbreviation	Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAT	Subsequent anticancer treatment
SBP	Systolic blood pressure
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
TTCD	Time to confirmed deterioration
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
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 patient-reported outcomes [PRO] and pharmacokinetics [PK] data) collected from Study G1T28-207, "PRESERVE 1: A Phase 3 Randomized, Double-blind Trial of Trilaciclib versus Placebo in Patients Receiving FOLFOXIRI/Bevacizumab for Metastatic Colorectal Cancer" protocol version 6.0.

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 PRO data collected in Study G1T28-207 will be written as a separate document, as will the SAP for PK data collected in this study.

1.1. Study Design

This is a randomized, double-blind, placebo-controlled, global, multicenter, Phase 3 trial evaluating the impact of trilaciclib on myeloprotection and anti-tumor efficacy when administered prior to FOLFOXIRI/bevacizumab in patients with proficient mismatch repair/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC) who have not received systemic therapy for metastatic disease. Patients will be randomly assigned (1:1) to receive placebo or trilaciclib on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (Induction). There will be three stratification factors for randomization: country, prior therapy in adjuvant/neoadjuvant setting, and presence of BRAF V600E mutation. Within each country, patient randomization will be stratified by history of systemic cytotoxic therapy in the adjuvant/neoadjuvant setting (yes/no) and BRAF V600E mutational status (yes/no). Study drugs administered during Induction are as follows:

- Trilaciclib (240 mg/m^2) or placebo – administered as a 30-minute IV infusion no more than 4 hours prior to chemotherapy on each day chemotherapy is administered. The second dose of trilaciclib/placebo should be administered as a 30-minute infusion on Day 2.
- Irinotecan 165 mg/m^2 –IV, Day 1

- Oxaliplatin 85 mg/m^2 – IV, Day 1
- Leucovorin 400 mg/m^2 – IV, Day 1; LEVOLeucovorin 200 mg/m^2 is an acceptable alternative
- Fluorouracil 2400 – 3200 mg/m^2 – continuous infusion over 46 – 48 hours beginning on Day 1; this dose range is provided to reflect geographic variations in prescribed fluorouracil (5FU) dose; however, the same dose should be continued throughout the study for each patient, except where dose modifications are required for toxicity management.
- Bevacizumab 5 mg/kg – IV, Day 1

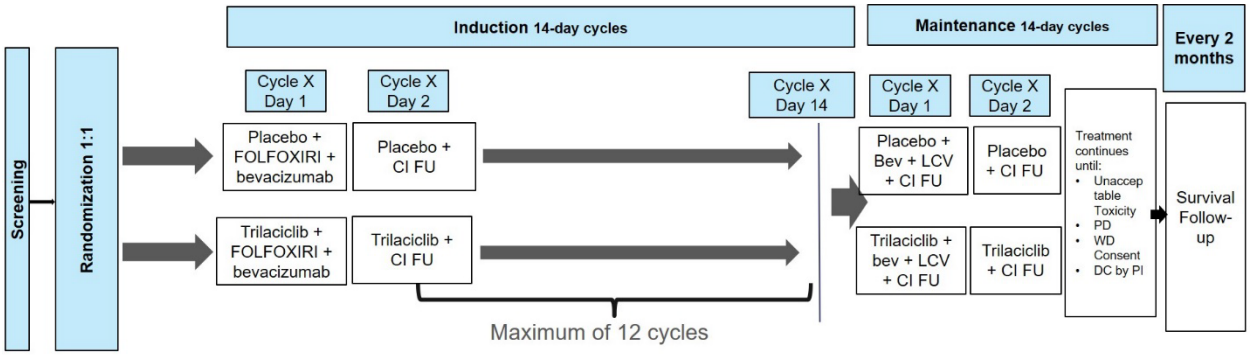
Though there is no requirement for a minimum number of chemotherapy cycles during Induction, patients should continue with Induction therapy (in the absence of disease progression) as long as it is tolerated. However, if a patient is unable to complete the maximum number of 12 Induction cycles because of toxicity, and the treating physician feels the patient will receive additional clinical benefit by transitioning to Maintenance, the patient will be allowed to discontinue oxaliplatin and irinotecan and continue on Maintenance therapy as described below.

Following completion of Induction, patients will continue in Maintenance, where they will receive trilaciclib or placebo per randomization allocation at study entry. Trilaciclib/placebo will be administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during Induction. The patient may continue to receive treatment on study until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the study, whichever occurs first. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons.

Upon discontinuation of study treatment, patients will be followed for survival, ie, patients or their caregivers will be contacted approximately every 2 months until the end of the study (or death) to record their status (alive or dead) as well as details of any subsequent systemic anti-cancer therapy initiated.

The general design of the study, including study drugs administration in Induction and Maintenance, is depicted in the design diagram below (Figure 1).

Figure 1: G1T28-07 Study Design Diagram



1.2. Study Objectives

Primary:

To assess the effects of trilaciclib on the neutrophil lineage compared with placebo in patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC.

Key Secondary:

- To assess the effect of trilaciclib on overall survival (OS) compared with placebo in patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC.

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

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	
• To assess the effects of trilaciclib on the neutrophil lineage compared with placebo in patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC.	• Duration of severe (Grade 4) neutropenia in Cycle 1– 4 of Induction • Occurrence of severe neutropenia during Induction
Key Secondary Objective	
• To assess the effect of trilaciclib on OS compared with placebo in patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC.	• OS

mCRC=metastatic colorectal cancer; OS=overall survival; pMMR/MSS=proficient mismatch repair/microsatellite stable

Other objectives and endpoints of the study can be found in Section 5 of the protocol.

1.3. Sample Size Consideration

The primary and key secondary objectives of this study are to evaluate the myeloprotection and anti-tumor efficacy of trilaciclib administered prior to FOLFOXIRI/bevacizumab (referred to as trilaciclib hereafter) compared with placebo administered prior to FOLFOXIRI/bevacizumab (referred to as placebo hereafter). To ensure strong control of family-wise Type I error rate at the level of 2-sided 0.05 when performing statistical analyses for the two primary myelosuppression endpoints and the anti-tumor efficacy endpoint, the overall 2-sided α of 0.05 will be split between the analyses of the primary endpoints (using $\alpha_1 = 0.04$) and analysis for OS (using $\alpha_2 = 0.01$).

The sample size is determined to support the primary efficacy analysis on the two primary efficacy endpoints. To detect the assumed treatment effect of an absolute reduction of 15% on the proportion of patients who have severe neutropenia (SN) in Induction at the significance

level of 2-sided 0.04 with 90% power, assuming the event rate for placebo is 25%, a sample size of 282 (141 per group) is needed using a Chi square test without continuity correction.

The sample size needed to detect a treatment effect on duration of SN (DSN) in Cycle 1-4 is estimated through simulations to detect a treatment effect of 2.4 days reduction for DSN in Cycle 1-4. In derivation of this endpoint, a duration of 0 will be assigned to patients who do not experience any SN in Cycle 1-4 (see details in Section 8.1.1). With a large proportion of 0 values, the variable of DSN in Cycle 1-4 does not follow a normal distribution but approximately a Poisson distribution with the mean parameter as -log (proportion of patients without any SN at Cycle 1-4). Assuming that approximately 80% of the SN occurring in Induction will take place in the first 4 cycles of Induction as reported in Rossini et al (Rossini, 2021) and assuming that trilaciclib will have an effect of 15% absolute reduction on SN in the first 4 cycles, it is estimated that the proportion of patients with SN in Cycle 1-4 is 20% for placebo and 5% for the trilaciclib group, respectively. Hence, the Poisson means are estimated to be 0.2231 and 0.0513 for placebo and trilaciclib groups, respectively. 10,000 trials were simulated based on the Poisson distributions to obtain the DSN in Cycle 1-4. Treatment group difference is evaluated using the Mann-Whitney-Wilcoxon test, and the power is estimated by the proportion of the trials that have achieved a 2-sided p-value ≤ 0.04 over 10,000 simulated trials. From the simulation results, a sample size of 200 patients (100 per group) can achieve an empirical power of 91%.

Overall, 282 patients (141 per group) are needed to detect the assumed treatment effect for each of the two co-primary myelosuppression endpoints with 90% power at the 2-sided significance level of 0.04. Assuming 5% of randomized patients will not have any post-baseline data, a total of 296 patients (148 per group) will be required for the study.

Although the number of patients is determined to ensure adequate power for the evaluation of the myeloprotection efficacy of trilaciclib, statistical comparisons for anti-tumor efficacy will also be conducted and the statistical significance is set to be 0.01 for testing treatment effect on OS. A total of 157 deaths are estimated to be observed during 52-months of study duration based on the following assumptions: 18 months of accrual and total duration of study of 52 months (34 months follow-up after the last patient is randomized), a hazard rate of 0.0029 for lost-to-follow up during the study, and the median OS of 31 months for placebo group (patients randomized to receive FOLFOXIRI/bevacizumab plus placebo) (Loupakis 2014). It is also assumed that the hazard ratio (trilaciclib vs. placebo) is 0.75 for OS.

A total of 44 patients from the Ukraine were randomized to the study as of February 2022. To mitigate the potential impact of the Russian-Ukraine war on data integrity and ensure the objectives of PRESERVE-1 will not be compromised, patients randomized from Ukraine prior to 09 September 2021 will be included in the efficacy analyses while all randomized patients from Ukraine will be included in the safety evaluation. As noted in the Protocol Amendment 4.0, there are 14 patients from Ukraine who have been randomized prior to 09 September 2021. That implies a total of 30 randomized patients from Ukraine will be excluded from the efficacy evaluation. To preserve the study power as it was originally designed, an additional 30 patients will be randomized in countries other than Ukraine. As such, the total sample size for this study will be 326. The reason that 09 September 2021 was chosen is because patients randomized prior

to this date would have completed or had the opportunity to complete the Induction per protocol (approximately 24 weeks), prior to the start of the war (24 February 2022).

2. THE NUMBER OF PLANNED ANALYSES

2.1. First Planned Analysis – Evaluation of Myeloprotection Efficacy and Effects on Patient Reported Outcome

As the protocol specifies, the first planned analysis would be conducted at the time when all randomized patients have finished up to 12 cycles of Induction treatment or discontinued during Induction. Trilaciclib's effects of myeloprotection and its effect on the PRO endpoints will be evaluated in this analysis. In addition, tumor responses will be assessed and safety data collected during Induction will also be analyzed at this time. The clinical study database will be locked to support this planned analysis.

At the time when all 326 patients have been randomized, the date when these patients will complete a maximum of 12 cycles Induction will be projected, and this projected date will be used as the data cutoff date (DCO) to determine inclusion of data elements to be locked in the study database. However, due to the possibility of cycle delays, the last few patients randomized might still be in later cycles (eg, Cycle 9 -12) of the Induction Period. In that event, the database will still be locked using the projected DCO to include all data collected in Induction as of the DCO, including the data from these patients who might still be ongoing in Induction.

At the time of performing the first planned analysis, the Sponsor will be unblinded to the results. However, Investigators and patients will remain blinded to individual patient's treatment assignment until the study is completed and the final study database is locked.

2.2. Second Planned Analysis - Analysis for Progression Free Survival

The second planned analysis of the study is to perform the PFS analysis around the time point that is 35 months post first randomization. This analysis will be performed based on a data snapshot.

2.3. Third Analysis – Analysis for Overall Survival

At the time when 157 death events are observed or at 52 months after the date of first randomization, whichever comes first, the study will be concluded, and the final study database will be locked to perform the OS analysis.

PFS analysis will also be performed at this time, as well as analyses of anti-tumor endpoints by cyclin-dependent kinase (CDK)4/6 biomarker signature as described in Section 8.2.9. Safety data will also be summarized at this time.

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.

3.2. The Modified Intent-to-treat Population

To account for potential data integrity issues resulting from the war in Ukraine, a modified intent-to-treat (mITT) population will be utilized as the primary analysis population for all efficacy evaluations.

The criteria for the patients in the ITT population to be included in the mITT population are as follows:

- All patients randomized in countries other than the Ukraine.
- All patients in the Ukraine who were randomized prior to 09 September 2021. This group should have completed, or had the opportunity to complete, Induction per protocol (approximately 24 weeks) prior to the start of the war (24 February 2022).

As a subset of the ITT population, the analyses performed on mITT will be consistent with the ITT principle, that is, data will be analyzed based on the randomly assigned treatment regardless of whether the patient received study treatment or was compliant with the protocol.

3.3. The Per-protocol Population

The Per-protocol (PP) Population is the subset of the mITT population that includes only those patients who have no major protocol deviations (that could significantly affect the accuracy of the study efficacy results) and who receive at least one dose of the randomly assigned study treatment. The PP population will be used to analyze selected critical myelosuppression endpoints whose outcomes are particularly susceptible to major protocol violations. Analyses on the PP population will be based on the randomly assigned treatment.

The criteria for major protocol deviations that will be used to justify the exclusion from the PP population will be fully defined and documented prior to the first study database lock. In addition, those randomized patients who will not be included in the PP population will be identified and documented with details prior to database lock.

3.4. The Response Evaluable Population

The Response Evaluable (RE) population includes those patients who are in the mITT population and received at least one dose of any study drug, have measurable (target) tumor lesion(s) at baseline tumor assessment, and have 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 tumor response evaluation.

3.5. 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. Unless otherwise specified, all safety data analyses will be performed on the Safety Population.

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, patients meeting entry criteria will be randomized at a 1:1 ratio to the treatment group of Placebo + FOLFOXIRI/bevacizumab or Trilaciclib + FOLFOXIRI/bevacizumab and thereafter enter the treatment phase of Induction. FOLFOXIRI stands for the set of chemotherapies of fluorouracil, leucovorin, oxaliplatin, and irinotecan and will be used in combination with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab. If not discontinued from study treatment during Induction, patients will enter the Maintenance phase of treatment and continue receiving trilaciclib or placebo per their randomization allocation at study entry, which will be administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during Induction. That is, the background treatments used in Maintenance are a continuation of the treatments used in Induction, with the exception of the two chemotherapies oxaliplatin and irinotecan. Study drugs in Maintenance will continue until one of the following conditions is met: disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the study, whichever occurs first.

Treatment cycles will occur consecutively within Induction, within Maintenance, as well as from Induction to Maintenance, without interruption except when necessary to manage toxicities or for administrative reasons.

An overview of treatment group descriptions by treatment phase that will be used in the SAP and TFLs with their corresponding descriptions in the protocol is provided in Table 2. In addition, the order of treatment groups that will appear 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
Induction	Placebo + FOLFOXIRI/bevacizumab	Placebo	Placebo + FOLFOXIRI/B	1
	Trilaciclib + FOLFOXIRI/bevacizumab	Trilaciclib	Trilaciclib + FOLFOXIRI/B	2
Maintenance	Placebo + 5FU/leucovorin/bevacizumab	Placebo	Placebo + 5FU/L/B	1
	Trilaciclib + 5FU/leucovorin/bevacizumab	Trilaciclib	Trilaciclib + 5FU/L/B	2
Overall treatment period (Induction and Maintenance) OR During the study	NA	Placebo	Placebo + Chemo/B	1
	NA	Trilaciclib	Trilaciclib + Chemo/B	2

FOLFOXIRI=fluorouracil, leucovorin, oxaliplatin, and irinotecan; B=bevacizumab, 5FU=fluorouracil, L=leucovorin. Chemo=fluorouracil, leucovorin, oxaliplatin, and irinotecan during Induction and fluorouracil and leucovorin during Maintenance.

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 characteristics will include an overall column for patients pooled from all treatment groups. In general, continuous variables will be summarized based on number of patients with non-missing data (indicated by n), mean, standard deviation, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number (n) and percentage of patients in each category.

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] onset date). Columns in listings will be ordered by treatment group, country, study site, patient identification (ID), 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 unless the collected data are integers. When the collected data are integers (whole numbers), the summary statistics of mean, median, Q1 and Q3 will be presented in the format with an additional digit after the decimal point. 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. The estimated adjusted relative risk will be reported with two decimal places.

For percentages, the total digits will be 3. That is, when the percentage has 2 digits prior to the decimal point, there will only be 1 decimal place (e.g., 30.5%); while for a percentage that has only 1 digit prior to the decimal point, 2 digits places will be presented after the decimal point (e.g., 0.16%).

P-values, in general, will be displayed in 3 decimal places, with the exception of when a p-value is less than < 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 Induction, during the overall treatment period (including Induction and Maintenance), or during the study (i.e., regardless of whether the patient was in Induction, Maintenance or Survival follow-up), 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 Induction is 12 cycles, which is equal to 168 days or 24 weeks or 5.54 months 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 Induction to Maintenance. For two special cases, 1) for the last Induction 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 Post Treatment Visit (PTV) as collected on the SCHEDULED VISITS CRF page. If the PTV does not occur for a patient, the End of cycle for the patient will be defined as 30 days post the last dose of any study drugs in the respective cycle.

Term	Definition
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 Induction (weeks)	Total number of weeks from Day 1 of Cycle 1 in Induction to the End of last Induction cycle. That is, (End of last Induction cycle – Day 1 of Cycle 1 + 1)/7.
Duration of overall study drug exposure (weeks)	The total number of weeks from Day 1 of Cycle 1 in Induction to the End of the last cycle in the study (could be in Induction or in Maintenance). That is, (End of the last cycle in the study – Day 1 of Cycle 1 + 1) / 7.
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 as alive. That is, duration of total follow-up = (date of death or date of last contact date known as 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.
- 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.

4.5. General Principles of Missing Data Handling

For primary and secondary efficacy endpoints (including key secondary), 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 onset or stop dates for AEs and medications/therapies will be adapted 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 onset or stop date and Section 5.4 for the rules of imputation of missing medication onset or stop dates.

For demographic and baseline characteristics, continuous variables will be summarized based on non-missing observations with the sample size of patients with non-missing data indicated. For a categorical variable with missing data, a category of "Missing" will be included as one of the components of the variable 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 randomized patient number 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.

In general, 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 three 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 an Induction treatment 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 in each respective group will be the denominator for calculating percentages of patients in each of the categories.

2. Study drug disposition

For the first planned analysis

For each study drug prescribed in Induction (trilaciclib/placebo, fluorouracil, leucovorin, oxaliplatin, irinotecan, and bevacizumab), the number and percentage of patients who were ongoing with the treatment during the Induction or discontinued the treatment during the Induction will be summarized by treatment group. In addition, for each of the 4 study drugs that could be continued from Induction to Maintenance per protocol (trilaciclib/placebo, fluorouracil, leucovorin, and bevacizumab), 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 received the respective study drug in each treatment group at Day 1 of Cycle 1 in Induction will be the denominator for the percentage calculation. Primary reasons for study drug discontinuation will be presented with the percentage of patients in each reason being calculated based on the number of patients who discontinued the study drug in Induction.

For the second planned analysis

At the time of performing the 2nd planned analysis, all patients should have finished Induction. For each of the 4 study drugs that could be prescribed in Maintenance (trilaciclib/placebo, fluorouracil, leucovorin, and bevacizumab) per protocol, the number and percentage of patients who were ongoing with the study drug in Maintenance or discontinued from the study drug during the study as of the DCO for performing the second planned analysis will be summarized

by treatment group. The number of patients who received the respective study drug in each treatment group at Day 1 of Maintenance Cycle 1 will be the denominator for the percentage calculation. Primary reasons for study drug discontinuation will also be presented with the percentage of patients in each reason being calculated based on the number of patients who discontinued the study drug in Maintenance.

For the final analysis

For each of the 6 study drugs (trilaciclib/placebo, fluorouracil, leucovorin, oxaliplatin, irinotecan, and bevacizumab), the number and percentage of patients who were discontinued from the study drug during the study will be summarized by treatment group. The number of patients who received the respective study drug in each treatment group at Day 1 of Induction Cycle 1 will be the denominator for the percentage calculation. Primary reasons for study drug discontinuation will also be presented with the percentage of patients in each reason being calculated based on the number of patients who discontinued the study drug during the study.

3. Study disposition

For the first planned analysis

Out of those who entered Induction (i.e., who were randomized and had at least one dose of any study drug, the Safety Population), the number and percentage of patients in the following mutually exclusive categories will be summarized by treatment group and overall: entered Maintenance, entered Survival follow-up without going through Maintenance, or discontinued from the study during Induction. The number of randomized patients who had at least one dose of any study drug in Induction in each respective group will be the denominator for calculating percentages of patients in each of the categories. 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.

For the secondary planned analysis

The number and percentage of patients who are ongoing in the study or discontinued from the study will be summarized by treatment group and overall for patients in the Safety Population. The number of patients who were randomized and had at least one dose of any study drug will be the denominator for the percentage calculation. The primary reason for study discontinuation will also be summarized by treatment group and overall, and the number of patients who discontinued in each group will be the denominator for the percentage calculation for each reason of discontinuation.

For the final analysis

The primary reasons for study discontinuation will be summarized by treatment group and overall for patients in the Safety Population. The number of patients who were randomized and had at least one dose of any study drug in the respective group will be the denominator for the percentage calculation.

4. Death

The number and percentage of patients who died as of the DCO for the respective analysis

(i.e., the first planned analysis, the second analysis, or the final analysis) will be summarized by treatment group and overall for all randomized patients along with the primary reason of death (Progressive Disease, AE, Other). The number of randomized patients in each respective group will be the denominator for calculating percentages of death, and the number of patients who died will be the denominator for calculating the percentage of patients for each reason of 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 only be summarized for the first planned analysis on the ITT and mITT population.

Demographics will be summarized descriptively by treatment group and overall. Demographics include age (at screening), age group (≥18 to <65, or ≥ 65; ≥ 18 to <70, or ≥ 70), gender, race, ethnicity, region, country.

Baseline disease characteristics will also be summarized descriptively by treatment group and overall. Baseline disease characteristics to be summarized include stage at screening, site of the primary tumor, primary tumor site laterality, Eastern Cooperative Oncology Group (ECOG) status, prior systemic therapy in adjuvant/neoadjuvant setting (abbreviated as Prior therapy hereafter), BRAF V600E mutation status (abbreviated as BRAF status hereafter), pMMR/MSS status with the methods used to determine pMMR/MSS status, and KRAS mutation status. All these baseline disease characteristics are categorical. For patients >70 years old, the total score from the G8 Health Status Screening Tool will also be summarized by treatment group and overall as a continuous variable.

Prior therapy and BRAF status are stratification factors and patients' status was entered into Interactive Web Response System (IWRS) at the time of randomization. These two factors were also entered into the electronic data capture (EDC) system. Therefore, Prior therapy and BRAF status as recorded in the IWRS and in the EDC will both be summarized and reported as baseline disease characteristics. However, as protocol specified, the status recorded in the IWRS will be used as the stratification factors for being included in statistical models to evaluate treatment effect unless otherwise specified.

Data listings for demographics and baseline disease characteristics for the ITT population will be produced, respectively. A separate data listing will be generated to present demographics collected for screen failures.

5.3. Medical History and Ongoing Conditions

Medical history and ongoing conditions at the Screening Visit will be summarized at the first planned analysis on the ITT population.

Non-cancer medical history and ongoing medical conditions collected at the Screening Visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later, and then summarized by treatment group and overall. 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 for ITT population.

5.4. Prior and Concomitant Medications

A summary of concomitant medications will be generated for the first planned analysis and the final analysis based on ITT population. Prior medications will be presented in a data listing.

Concomitant medications are those medications that were given during the time interval from the first dose of any study drug to the end of last cycle for the respective analysis. 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 202109.

Concomitant medications will be summarized by ATC and PT and presented in a descending order of frequency for ATC and PT within an ATC based on the overall group. 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, respectively.

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 for concomitant medications that are not ongoing at the time of data cutoff:

- 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 an indicator for prior or concomitant for the ITT population.

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 CSR. 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 the ability of assessing efficacy and safety of the investigational drug. Criteria that define major or minor protocol deviations will be specified, documented, and signed off 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 and unblinding. These cases will impact on the composition of the Safety population and a data listing for these patients will be provided and included in the CSR.

5.5.2. Summary of Protocol Deviations

A protocol deviation summary will be generated for the first planned analysis (including protocol deviations occurring during Induction) and for the final analysis (including all protocol deviations occurred since Induction).

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 flags for major or minor for the ITT population.

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

Prior anticancer therapies refers to those anticancer treatments that patients received prior to the Screening Visit, including medications, surgical procedures, or radiotherapy treatments. Concomitant anticancer therapies refer to those treatments, other than study drugs, that could be utilized concurrently with study drug(s) as specified in the protocol. That is, the treatments that were given in the time interval from the first dose of any study drug to the end of last cycle in the respective analysis. Subsequent anticancer 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 onset or stop dates for medications described in Section 5.4 are, in general, applicable for missing onset 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 only be generated for the first planned analysis and based on the ITT population.

The number and percentage of patients with any prior anticancer therapies will be summarized by treatment group and overall. Prior systemic 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 colorectal cancer and radiotherapies will be summarized by treatment group and overall, respectively.

Data listings will be produced for all prior anticancer therapies, including detailed information related to prior systemic anticancer therapies such as setting, regimen, start/stop dates, and detailed information related to surgical procedures and radiotherapies for the ITT population.

6.2. Concomitant Anticancer Therapies

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

The number and percentage of patients receiving any concomitant anticancer surgical procedures or radiotherapies will be summarized by treatment groups and overall, respectively.

Detailed information for surgical procedures and radiotherapies will be included in the data listing for ITT population.

Summary of Palliative Therapies Administered While on Study Treatments

The study protocol allowed patients to receive palliative therapies (through radiotherapy or surgeries/procedures) during the study. Palliative therapies will be summarized at the first planned analysis and at the final analysis for the mITT population.

Patients with palliative therapy administrations will be identified based on blinded Sponsor medical review of details entered into the eCRF pages of "Concurrent radiotherapy", "Concurrent surgeries/procedures", "Subsequent radiotherapy" or "Subsequent surgeries/procedures". A palliative therapy for a patient will be included in the first analysis if the date of the administration is less than or equal to the last date in Induction for that patient, regardless of whether it is entered to a concomitant or subsequent page of the eCRF. This is because the end date of Induction is defined as the date of PTV, if it exists, or 30 days post the last dose date of any study drugs in Induction. Palliative therapies used during the time interval from last dose of any study drugs to the last date in Induction were entered to subsequent (radiotherapy or surgeries/procedures) eCRF pages.

The number and percentage of patients who have had any palliative therapies (either through radiotherapy or surgeries/procedures) during the reporting interval will be summarized by treatment group and overall. In this summary, a patient who has more than one administration of palliative therapies (including radiotherapy or surgeries/procedures) will only count once. In addition, the number and percentage of patients receiving radiotherapy or surgeries/procedures for palliative purposes during the reporting interval will also be summarized by treatment group and overall.

6.3. Subsequent Anticancer Treatments

Subsequent anticancer treatments (SAT) will be summarized at the final analysis based on the ITT population.

The number and percentage of patients receiving at least one SAT in any modality (systemic anticancer therapies, surgical procedure, or radiotherapy) as well as for each of the modalities will be summarized by treatment group and overall.

For the subsequent systemic anticancer therapies, the total number of lines of therapy will be summarized by treatment group and overall as a continuous variable, and the number and percentage of patients who had 1, 2, .. maximum lines of systemic anticancer therapies will also be summarized. The number of patients who had at least one dose of any systemic anticancer therapies will be the denominator to calculate the percentage for the respective group. Furthermore, subsequent systemic anticancer therapies will be summarized by treatment group based on ATC and PT and presented in a descending order of frequency for ATC and PT within an ATC based on the overall group. The best overall response to each treatment regimen and disease progression status as collected will be presented in data listings.

Analysis for Patients who Undergo Curative Intent Surgical Procedure during the Study

Patients with metastases confined to the liver who experience a robust response to chemotherapy may also proceed with curative intent surgical resection at the Investigator's discretion. In that event, study drugs will be discontinued before they undergo such surgery. If choosing to stay with the study after the surgery, these patients would enter the Survival Follow-up period of the study. These patients will be identified based on blinded Sponsor medical review of the terms provided in the eCRF pages of "Subsequent surgery" . The number and percentage of patients with curative intent surgical procedure will be summarized by treatment group and overall for the ITT population. Because this patient population has a better prognosis for tumor response

outcomes, the SAT received by this patient group will not be included in the above stated SAT summaries.

Subsequent anticancer treatment in any format (systemic anticancer therapies, surgical procedure, or radiotherapy) for this group of patients will be presented in data listings. If this group contains at least 10% of all randomized patients in the study, their SAT will be summarized separately in a similar manner as described above.

Corresponding data listings will be provided for ITT population.

7. STUDY DRUG EXPOSURE, DOSE INTENSITY AND MODIFICATION

7.1. Duration of Study Drug Exposure

Analyses described in this section will be based on the Safety population unless otherwise specified.

7.1.1. Duration of Study Drug Exposure in Induction

Duration of study drug exposure (weeks) in Induction is defined as the duration from Day 1 of Cycle 1 in Induction to the End of cycle for the last cycle in Induction. That is, duration of study drug exposure in Induction (weeks) = (End of cycle for the last Induction cycle – Day 1 of Induction 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 Induction will be summarized by treatment group and overall. For each treatment group, the total number of cycles that a patient received will be summarized as a continuous variable, as well as a categorical variable. That is, descriptive summary statistics will be provided for the total number of cycles that patients received, and the number and percentage of patients that received exactly 0, 1, 2,…, up to the maximum number of cycles will also be summarized.

Corresponding data listings will be provided.

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

Two additional variables will be calculated to report study drug exposure: the duration of study drug exposure in Maintenance and the duration of total study drug exposure (i.e., Induction and Maintenance combined exposure). These will be calculated and reported at the second planned analysis and the final analysis. Specifically:

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

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

For the patients in the Safety population who enter Maintenance, the duration of study drug exposure in Maintenance will be calculated and summarized by treatment group and overall. For each treatment group, the total number of cycles that a patient received will be summarized as a continuous variable, as well as a categorical variable.

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 will be summarized as a continuous variable, as well as a categorical variable.

Corresponding data listings will be provided.

7.2. Cumulative Dose and Dose Intensity

Dose administration parameters will be summarized for Induction and the overall treatment period, respectively. That is, the analyses described in this section will be performed at the first planned analysis, the second planned analysis, and the final analysis, respectively.

At each specified analysis time, the dose administration during the respective time interval (Induction, or overall treatment period) as defined in Table 3 (Section 4.3) will be used to calculate dose intensity.

The definitions for cumulative delivered dose, delivered dose intensity, relative cumulative dose, and relative dose intensity at the patient level, along with other parameters involved in the calculation of these variables are presented in Table 4. All collected dose information will be used in the calculation.

The calculated cumulative delivered dose, delivered dose intensity, relative cumulative dose, and relative dose intensity will be summarized by treatment group as continuous variables.

All variables described in Table 4 will be included in the data listing except for the study drug administration schedule.

Table 4: Dose Administration Parameters for Study G1T28-207

Parameter	Meaning	Trilaciclib	Fluorouracil	Leucovorin	Oxaliplatin	Irinotecan	Bevacizumab
Study drug administration schedule	Drug dose and schedule per protocol	240 mg/m^2 IV on Days 1 and 2 of a 14-day cycle	2400 – 3200 mg/m^2 IV given via 46-48 hour continuous infusion beginning on Day 1of a 14-day cycle	400 mg/m^2 IV on Days 1 of a 14-day cycle; 200 mg/m^2 is also acceptable	85 mg/m^2 IV on Day 1 of a 14-day cycle	165 mg/m^2 IV on Day 1 of a 14-day cycle	5 mg/kg IV on Day 1 of a 14-day cycle
Cumulative delivered dose (mg/m^2 or mg/kg)	Sum of doses over the duration of the study drug administration	Sum of doses over the duration of trilaciclib/placebo administration (mg/m^2)	Sum of doses over the duration of fluorouracil administration (mg/m^2)	Sum of doses over the duration of leucovorin administration (mg/m^2)	Sum of doses over the duration of oxaliplatin administration (mg/m^2)	Sum of doses over the duration of irinotecan administration (mg/m^2)	Sum of doses over the duration of bevacizumab administration (mg/kg)
Delivered Dose Intensity (mg/m^2/week or mg/kg/week)	Cumulative dose administered per week	Cumulative dose (mg/m^2) / duration of study drug exposure in weeks [(mg/m^2/week)]	Cumulative dose (mg/m^2) / duration of study drug exposure in weeks [(mg/m^2/week)]	Cumulative dose (mg/m^2) / duration of study drug exposure in weeks [(mg/m^2/week)]	Cumulative dose (mg/m^2) / duration of study drug exposure in weeks [(mg/m^2/week)]	Cumulative dose (mg/m^2) / duration of study drug exposure in weeks [(mg/m^2/week)]	Cumulative dose (mg/kg) / duration of study drug exposure in weeks [(mg/kg/week)]
Relative cumulative dose (%)	Cumulative delivered dose over cumulative prescribed dose	[Cumulative delivered dose (mg/m^2) / (240 × 2 × number of cycles) (mg/m^2)]*100	[Cumulative delivered dose (mg/m^2) / (starting dose × number of cycles) (mg/m^2)] *100	[Cumulative delivered dose (mg/m^2) / (starting dose × number of cycles) (mg/m^2)] * 100	[Cumulative delivered dose (mg/m^2) / (85 × number of cycles) (mg/m^2)] * 100	[Cumulative delivered dose (mg/m^2) / (165 × number of cycles) (mg/m^2)] * 100	[Cumulative delivered dose (mg/kg) / (5 × number of cycles (mg/kg)] * 100
Relative dose intensity (%)	Delivered dose intensity over prescribed dose intensity	[Delivered dose intensity/480/2]*100	[Delivered dose intensity / starting dose /2)]*100	[Delivered dose intensity / (starting dose/ 2)]*100	[Delivered dose intensity / (85 /2)]*100	[Delivered dose intensity / (165 / 2)]*100	[Delivered dose intensity / (5/2)]*100

IV = intravenous.

7.3. Study Drug Modifications

Study drug modifications will be summarized for Induction and for the overall treatment period, respectively. That is, the analyses described in this section will be performed at the first planned analysis and the final analysis, respectively.

There are three types of study drug modification: dose reduction, cycle delay or infusion interruption. Protocol permitted dose reductions for each study drug are summarized in Table 5.

Table 5: Protocol Permitted Dose Reduction by Study Drug

Study Drug	Number of Dose Reductions Allowed
Trilaciclib/placebo	0
Fluorouracil	2
Leucovorin	0
Oxaliplatin	2
Irinotecan	2
Bevacizumab	0

Study drug modifications will be summarized by treatment group based on the Safety population in each of the following categories: chemotherapy dose reduction, treatment cycle delay, and infusion interruption. The number and percentage of patients who had any chemotherapy dose reduction, any cycle delay, cycle delay due to hematological toxicity, or any infusion interruption will be summarized by treatment group.

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

Dose reduction for a specific chemotherapy. Three chemotherapies (fluorouracil, oxaliplatin, and irinotecan) can have dose reduction per protocol (Table 5). Of these, only fluorouracil is used during the entire treatment period. Dose reduction is counting for all the reductions across these three chemotherapies during the reporting period. Although the protocol specified up to 2 reductions for each of the three chemotherapies, there were protocol deviations of additional reductions. All of these will be included in the summary of dose reductions. The number and percentage of patients who had at least one dose reduction will be summarized by treatment group. In addition, the number and percentage of patients will be summarized by treatment group in the following mutually exclusive categories: no chance to have any dose reduction (Cycle 1 treatment only), 0, 1, 2, up to the maximum number of reductions for the drug. The reasons for dose reduction as collected in the eCRF will also be summarized for each of these chemotherapies 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 as a continuous variable by treatment group. In addition, the number and percentage of patients in each of the following mutually exclusive categories will be summarized by treatment group: no chance to have any cycle delay (Cycle 1 treatment only), 0, 1, 2, …, up to the maximum number of delays.

The reasons for cycle delay collected in eCRF are as follows:

Absolute neutrophil count (ANC) value < 1.0×10^9/L, platelet counts < 75 x 10^9/L, Other hematologic toxicity, Non-hematologic toxicity, or Other. Patients with reasons entered under the "Other" category will be further classified based on medical review of comments collected on the eCRFs into the following categories:

- Administrative
- Concurrent Illness or Procedure
- COVID-19 Infection or Site Closure
- Patient's Decision
- Principal Investigator's Decision
- Other
- Missing

All these categories (eCRF collected and further classified) will be reported by treatment group. The percentage of patients in each of the categories will be calculated based on the number of patients in the respective treatment group in the Safety population.

Infusion interruption. Infusion interruption was captured in the eCRF for each respective study drug with the reasons. In addition to summarizing the number and percentage of patients who had at least one infusion interruption for any study treatment, the summary statistics for the total number of infusion interruptions and the number and percentage of patients in each of the following mutually exclusive categories will be summarized by treatment group: 0, 1, 2, …, up to maximum number of interruptions. The number of interruptions is the sum of infusion interruptions for all study drugs for which the interruption occurred at least once during the infusion across all cycles in Induction. Multiple interruptions for a drug during an infusion will only be counted once. The reasons for infusion interruption as collected in the eCRF will also be summarized by treatment group.

Furthermore, trilaciclib/placebo infusion interruption and the reasons will also be summarized in the similar manner described above.

Corresponding data listings will be provided.

7.4. Duration of Total Follow-up

Duration of total follow-up will be summarized for the final analysis.

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 summary 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 8.2.4.3.

8. EFFICACY ANALYSIS

Trilaciclib's myeloprotection efficacy and its effect on PRO endpoints will be evaluated based on the data collected during Induction. Data for the PRO instrument Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) collected as of the DCO determined for the first study database lock will be included in the first study database to derive the key secondary endpoint, time to deterioration of fatigue. Trilaciclib's effect on tumor response will be evaluated on data collected during Induction in the first planned analysis, and it will also be assessed at the time when PFS is analyzed in the cumulative manner.

Treatment effects on PFS and OS will be event-driven. When the number of events as specified in Sample Size Consideration (Section 1.3) are observed for PFS and OS, the clinical database will be locked accordingly to support the analysis of PFS and OS, either at the same time or at two separate times (see Section 2.2 and Section 2.3).

For the patients who will undergo curative intent surgical resection due to response to study treatments, study drugs will be discontinued before the surgery per protocol. As such, there will be no myelosuppression assessments or PRO data collection following the curative intent surgery procedure. After the surgery, these patients can continue with the study in the Survival Follow-up period, and they might have continued tumor assessments as specified in the protocol for all who entered the Survival Follow-up period. However, tumor assessments collected after the date of curative intent surgical procedure will be excluded from derivation of tumor response status, duration of response, and PFS for these patients. On the other hand, the status of this procedure will not impact on the derivation of OS for these patients.

8.1. Definitions of Efficacy Endpoints

Efficacy endpoints defined in this section will be derived for patients in the mITT population.

8.1.1. Primary Efficacy Endpoints – Duration of Severe Neutropenia in Cycle 1-4 and Occurrence of Severe Neutropenia during Induction

Severe neutropenia 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).

The co-primary endpoint DSN in Cycle 1-4, is defined as the days of the first SN event that occurred in the first 4 cycles of Induction. Specifically, for patients with at least 1 SN event in Induction Cycle 1, 2, 3 or 4, DSN in Cycle 1-4 is calculated for the first occurrence of the event following the rules described below.

- For patients whose SN is resolved (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 the cycle), DSN 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 with unresolved neutropenia, DSN will be derived as the total number of days from the date of the first SN occurrence to the date of withdrawal (the last day of the study).

For patients without any SN in the first 4 cycles of Induction or those who were in the mITT population but who did not receive any study drug, DSN in Cycle 1-4 will be set to 0.

In Cycle 1, hematology laboratory parameters, including ANC, will be collected at Day 1 (prior to dosing), Days 2, 4, 6, 8, 10, 12 and at the End of Cycle 1 (See Table 3 in Section 4.3 for End of cycle definition). In Cycle 2 to 4, ANC will be collected at Day 1 and Day 8 of each cycle. For the patients who experienced SN in a treatment cycle, unscheduled assessments of ANC must be obtained in that cycle to evaluate the status of SN resolution, since the event must be resolved before the patient could start next cycle's treatment. All scheduled and unscheduled ANC assessments obtained in Cycle 1, 2, 3, or 4 will be used to calculate the DSN in Cycle 1-4 for those patients with at least 1 SN event in the first 4 cycles of Induction.

DSN in Cycle 1-4 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 SN during Induction (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 Induction regardless of scheduled or unscheduled visits. Occurrence of SN is a binary random variable (Yes or No).

8.1.2. Key Secondary Efficacy Endpoint – Overall Survival

OS 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 for final database lock (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 or undergoes curative intent surgical resection.

8.1.3. Secondary Endpoints – Other Myelosuppression Endpoints

Secondary myelosuppression endpoints that are defined to assess trilaciclib's effect on multiple lineage protection in Induction are described in Table 6 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 evaluate trilaciclib's impact on chemotherapy delivery in Induction are also described in Table 6.

Unless otherwise specified, all endpoints described in Table 6 are derived based on data collected through scheduled and unscheduled visits during Induction.

Table 6: Other Myelosuppression Endpoints

Lineage	Endpoint	Type of Variable
Neutrophils	Number of cycles with severe neutropenia (event rate per 100 cycles)	Counting
	Occurrence of febrile neutropenia	Binary
	Occurrence of GCSF administration	Binary
	Number of cycles with GCSF administrations (event rate per 100 cycles)	Counting
	Occurrence of Grade 3 or 4 neutropenia	Binary
RBCs	Occurrence of Grade 3 or 4 decreased hemoglobin	Binary
	Occurrence of RBC transfusion on/after Week 5	Binary
	Number of RBC transfusions on/after Week 5 (event rate per 100 weeks)	Counting
	Occurrence of ESA administration	Binary
Platelets	Occurrence of Grade 3 or 4 decreased platelet counts	Binary
	Occurrence of platelet transfusion	Binary
	Number of platelet transfusions (event rate per 100 weeks)	Counting
All three lineages	Occurrence of Grade 3 or 4 hematologic laboratory values	Binary
Chemotherapy Modifications	Occurrence of chemotherapy dose reduction (all causes)	Binary
	Number of chemotherapy dose reductions (event rate per 100 cycles)	Counting
	Occurrence of cycle delay due to toxicity	Binary
	Number of cycle delays due to toxicity (event rate per 100 cycles)	Counting

ESA=erythropoiesis-stimulating agents; GCSF=granulocyte colony stimulating factor; RBC=red blood cell

8.1.3.1. Neutrophil-Related Endpoints

Number of Cycles with Severe Neutropenia

The number of cycles with SN in Induction for a patient is the total number of cycles in Induction where the patient had at least one SN event. For patients who did not have any SN during Induction and those who were in the mITT population 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

FN is an AE as reported by the Investigator and captured in the eCRF. A PT term 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 Induction and is a binary random variable (Yes or No).

Occurrence and Number of Granulocyte Colony Stimulating Factor (GCSF) Administrations

Administration of GCSF is collected throughout Induction. Cycles where GCSF was administered will be identified by comparing the start and stop dates of each administration of GCSF to cycle interval. If any of the time intervals in which GCSF 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 GCSF administration. Data handling conventions for missing start and stop dates are described in Section 5.4.

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

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

- If the start date and stopped date both were on Cycle X Day 1, it will be counted an occurrence in Cycle X – 1 only (assuming the trigger event occurred in Cycle X-1).
- If the start date was on Cycle X Day 1 and stop date was within the same cycle or in a later cycle, Cycle X-1 will be included in the total count of cycles in which GCSF was administrated as the triggering event is considered to have occurred in Cycle X-1.
- If the start date was in the middle of Cycle X-1 (that is, any day other than Cycle X-1 Day 1 or end of Cycle X-1), and the stopped date was on Day 1 of Cycle X, it will only be counted an occurrence in Cycle X-1.

For patients who did not have any GCSF use during Induction and those who were in the mITT population but did not receive any study treatment, the value of 0 will be assigned. Number of cycles with GCSF administrations is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

Occurrence of Grade 3 or Grade 4 Neutropenia

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

8.1.3.2. RBC-Related Endpoints

Occurrence of Grade 3 or 4 Decreased Hemoglobin

Occurrence of Grade 3 or 4 decreased hemoglobin (Hgb) in Induction 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 Induction. It is a binary random variable (Yes or No).

Occurrence and Number of RBC Transfusion on/after Week 5

The following endpoints will be derived for those patients who had at least 4 weeks of study drug exposure, which is equivalent to having at least 29 days exposure in Induction.

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 (relative to Day 1 of Cycle 1) during Induction. 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 Induction. 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 Induction and those who were in the mITT population 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 Induction. 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 Induction for a patient is defined as having at least one cycle in which ESA was administrated for the patient during Induction. It is a binary random variable (Yes or No).

8.1.3.3. 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 Induction. 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 Induction. 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 Induction. Transfusions with a unique start date during Induction were counted as different events. For patients who did not have any platelet transfusion in Induction and those who were in the mITT population 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.

8.1.3.4. All Three Lineages

Occurrence of Grade 3 or 4 Hematologic Laboratory Values

Occurrence of Grade 3 or 4 hematologic laboratory values (abbreviated as occurrence of Grade 3 or 4 hem-labs) for a patient is defined as having at least one ANC $< 1.0 \times 10^9$/L, Hgb <8.0 g/dL, or platelets $< 50.0 \times 10^9$/L based on the CTCAE toxicity criteria among all scheduled or unscheduled assessments during Induction. It is a binary random variable (Yes or No).

8.1.3.5. 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 Induction (regardless of which chemotherapy). Chemotherapies that allow dose reduction and the maximum number of reductions in Induction can be found in Section 7.3. 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 counts of chemotherapy dose reductions across the 3 chemotherapies for which dose reduction was allowed per protocol (Table 5) during Induction. In addition, chemotherapy that was stopped due to toxicity will be also counted as a dose reduction event. The value of 0 will be assigned to those patients who did not have any chemotherapy dose reductions during Induction and those who were in the mITT population but did not receive any study treatment. Number of chemo-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: ANC value $< 1.0 \times 10^9$/L, platelet counts $< 75 \times 10^9$/L , Other hematologic toxicity, Non-hematologic toxicity, or Other. A cycle that was marked as delayed with the reason of ANC value $< 1.0 \times 10^9$/L, platelet counts $< 75 \times 10^9$/L , or Other hematologic toxicity is considered a delay due to 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 Induction 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 such reason for the patient during Induction. For patients who did not have any cycle delays due to hematologic toxicity in Induction and those who were in the mITT population but did not receive any study treatment, the value of 0 will be assigned. Number of cycle delays due to toxicity is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

8.1.4. Secondary Endpoints – Healthcare Utilization

Secondary endpoints that are defined to assess trilaciclib's impact on healthcare utilization are listed below.

- Occurrence of all-cause hospitalizations
- Occurrence and number of hospitalizations due to CIM, Sepsis or Other Serious Infections
- Occurrence of intravenous antibiotic administration

Occurrence of All-cause Hospitalizations

Hospitalization is collected as one of the serious adverse events (SAEs) in eCRF along with the cause of the hospitalization, which are captured in PTs. If a patient was hospitalized and several

PTs were attributed to that hospitalization with the same start date, there will be just one count for the corresponding hospital event.

Occurrence of all-cause hospitalization for a patient is defined as having at least one hospitalization regardless of cause during Induction. It is a binary random variable (Yes or No).

Occurrence and Number of Hospitalizations due to CIM, Sepsis or Other Serious Infections

Myelosuppression events that were related to chemotherapy are grouped in three categories: Neutropenia (including PT terms of Nneutropenia, Neutrophil count decreased, and Febrile neutropenia), Anemia (including PT terms of Anemia, Anaemia, Anaemia macrocytic, Red blood cell count decreased, Hemoglobin decreased, and Pancytopenia), and Thrombocytopenia (including PT terms of Thrombocytopenia and Platelet count decreased).

Hospitalization that was caused by any of these events is defined as hospitalizations due to CIM.

The criterion for identifying the proper infection SAE records is as follows: if the SOC from MedDRA (Version 24.1) takes value "INFECTIONS AND INFESTATIONS", and the AE is a serious event.

Occurrence of hospitalization due to CIM, sepsis or other serious infections for a patient is defined as having at least one hospitalization due to CIM, sepsis or other serious infections during Induction. It is a binary random variable (Yes or No).

Number of hospitalizations due to CIM, sepsis or other serious infections for a patient is defined as the total number of hospitalizations due to any of these causes during Induction. In deriving the total number of hospitalizations, if a hospitalization start date is after the discharge date of previous hospitalization which was caused by the same AE, it will be counted as a new hospitalization event. The value of 0 will be assigned to those patients who did not have any hospitalizations due to CIM, sepsis or other serious infections during Induction and those who were in the mITT population but did not receive any study treatment. Number of hospitalizations due to CIM, sepsis or other serious infections is a counting random variable and the summary statistics for this variable is event rate per 100 cycles.

Occurrence of Intravenous Antibiotic Administration

IV antibiotic administration is collected as concomitant medications which are coded using WHO-DD version WHODrug-Global-B3 202109. The criteria for identifying an IV antibiotic administration event are:

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

Occurrence of IV antibiotic administration for a patient is defined as having at least one IV antibiotic administration during Induction, and it is binary random variable (Yes or No).

8.1.5. Secondary Endpoint – Progression Free Survival

Progressive disease (PD) and tumor response status are programmatically determined according to Response Evaluable Criteria in Solid Tumors (RECIST) v1.1 based on the radiographic tumor assessment data 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.

PD and death due to any cause are referred to as PFS events. The observation of PFS events is not limited to a specific treatment phase (Induction, 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.

Details for PFS calculation and censoring rules can be found in Table 7.

Table 7: PFS Calculation 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 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 or the date of initiation of subsequent anticancer treatment	Censored
Underwent curative intent surgical procedure during the treatment period of the study	Date of last adequate radiologic assessment prior to the date of surgery	Censored
Required palliative therapies	Date of last adequate radiologic assessment prior to the date of the first palliative therapy	Censored

8.1.6. Secondary Endpoints – Tumor Response and Duration of Objective Response

Secondary anti-tumor efficacy endpoints include the following, which will be calculated and reported twice during the study: at the first planned analysis (including all tumor assessments collected in Induction) and at the time when PFS is analyzed (including all tumor assessments collected as of the DCO for the analysis if it is not final).

For the patients who underwent a curative intent surgical procedure due to response to study treatments, study drugs will be discontinued before the surgery per protocol. After the surgery, these patients can continue with the study in the Survival Follow-up period. As such, they might have continued tumor assessments as the protocol specified for all who entered the Survival Follow-up period. However, tumor assessments collected after the date of curative intent surgical procedure will be excluded from derivation of tumor response status and duration of response.

For patients who required palliative treatment concomitantly while on study drugs, tumor assessments after the date of first palliative treatment administration will be excluded from tumor response evaluation.

Tumor scan data collected in Induction are the basis to classify tumor response status for being analyzed in the first planned analysis, and the tumor scan data collected as of DCO for the PFS analysis are the basis to classify tumor response status for being analyzed in the second planned analysis.

- Best overall response (BOR)
- Objective response rate (ORR)
- Duration of objective response (DOR)

At each tumor assessment visit, an overall time point response status based on 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.

Tumor assessments collected in Induction (for the first analysis) or by the DCO (for the second analysis) will be used to determine response status, with the following rules of exclusion: (i) assessments obtained after radiographic disease progression; (ii) assessments obtained after initiation of any subsequent anti-cancer therapy, including undergoing curative intent surgical procedure; (iii) assessments obtained after the first dose of palliative therapies.

<u>Best Overall Response</u>

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), PD, and Not Evaluable (NE). The minimum duration of stable disease must be 7 weeks starting from the date of randomization (the protocol scheduled tumor assessments is every 8 weeks ± 1 week during Induction and every 12 weeks ± 14 days during Maintenance).

Objective Response Rate

Achieving an objective response for a patient is defined as having a complete response (CR) or partial response (PR) as the BOR. ORR is defined as the proportion of the patients who achieved objective response based on the RE population.

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 treatment is 7 weeks (the protocol scheduled tumor assessments is every 8 weeks ± 1 week). 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 Confirmed Objective Response

DOR is calculated for patients who achieved confirmed CR or 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 CR or PR + 1)/30.4375.

Censored DOR follows the same rules as the censoring rules for PFS (see Section 8.1.5).

8.1.7. Secondary Endpoint - Time to First Confirmed Deterioration of Fatigue

The secondary PRO efficacy endpoint is time to confirmed deterioration (TTCD)-fatigue, where fatigue is the total score calculated from the PRO instument FACIT-F (13 item subscale of the Functional Assessment of Cancer Therapy – Anemia [FACT-An]). The confirmed clinically meaningful deterioration for fatigue in Induction is defined as such an event where the fatigue score obtained in Induction was at least 7 units worse compared with the baseline, and it was confirmed by the fatigue score collected at the next scheduled visit (which can go beyond Induction). Of note, the value of 7, defining the threshold of clinically meaningful deterioration of fatigue in this patient population, was determined by the anchor analysis conducted on the pooled, blinded data at the time when 50% of the randomized patients had finished Induction. The SAP for the anchor analysis as a separate document were submitted to the Food and Drug Administration (FDA) via the Sponsor response to a Type C Written Response Only, dated 10-Aug-2021; and the results from anchor analysis were submitted to the FDA on 16-Sep-2022 as the Background Materials to support a Type C teleconference held with FDA on 27-Oct-2022.

If the patient discontinued from the study (including death) or missed all PRO assessments after the first deterioration was observed, the one-time observation of deterioration will be classified as a confirmed event. All FACIT-F data collected as of the data cutoff date for the first study database lock will be included in the TTCD-fatigue derivation following the rules described above.

For the patients with one confirmed clinically meaningful deterioration for fatigue, TTCD-fatigue (months) will be calculated as the time from the date of randomization to the date of the first confirmed clinically meaningful deterioration in the unit of months. That is, TTCD-fatigue (months) = (Date of assessment when the first confirmed clinically meaningful

deterioration was observed – Date of randomization + 1)/30.4375.

For patients who did not experience a confirmed clinically meaningful deterioration prior to the data cutoff date for the first planned analysis, the censored TTCD-fatigue will be calculated using the date of the last available PRO assessment (i.e., the assessment with last non-missing value) as the end date. Patients with no baseline assessment, with no post-baseline assessments, or whose baseline scores did not allow for further deterioration will be censored at the date of randomization.

8.2. Statistical Analysis Methods

8.2.1. General Considerations for Efficacy Analysis

Unless otherwise specified, all efficacy analyses will be performed on the mITT population.

Unless otherwise specified, the treatment effect on myelosuppression endpoints will be evaluated based on the data collected during Induction, and the treatment effect on PRO endpoints will be evaluated using all available data as of the DCO for the first database lock. The first planned analysis is to evaluate trilaciclib's myeloprotection effect and its effect on PRO endpoints compared with placebo for patients receiving FOLFOXIRI/bevacizumab for pMMR/MSS mCRC. The analysis for PFS or OS will not be included in the first planned analysis since the expected number of events for either PFS or OS (see Section 1.3) will not be reached at the DCO for the first study database lock.

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

There are three stratification factors for randomization: country, prior therapy in adjuvant/neoadjuvant setting, and BRAF V600E mutational status. Within each country, patient randomization will be stratified by history of prior therapy in the adjuvant/neoadjuvant setting (Yes or No) and BRAF V600E mutational status (Yes or No). History of prior therapy in the adjuvant/neoadjuvant setting will be abbreviated as "Prior chemotherapy" and BRAF V600E mutational status will be abbreviated as "BRAF status" hereafter. Countries will be grouped into the factor of "Region" with four different entries of US, Eastern Europe, Western Europe, and China. The factor "Region" will be used instead of "country" in the statistical analysis models to account for regional differences in clinical practice.

It is anticipated that all three factors (Region, Prior chemotherapy and BRAF status) will have an impact on patients' anti-tumor efficacy outcomes, but only Region and Prior chemotherapy will have an impact on myeloprotection efficacy. Therefore, Region and Prior chemotherapy will be included as the factors in statistical analysis models evaluating trilaciclib's effect on myeloprotection and trilaciclib's effect on PRO endpoints, while all three 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 except for "region" 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 0.05 is strongly controlled among statistical analyses for primary and key secondary endpoints. 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. Overarching Statistical Approaches to Ensure Strong Control of Family-wise Type I Error Rate among Statistical Analysis for Two Primary and One Key Secondary Efficacy Endpoint

To ensure strong control of family-wise Type I error rate at the level of 2-sided 0.05 when performing statistical analyses for the two primary myelosuppression endpoints (DSN in Cycle 1-4 and occurrence of SN during Induction) and OS, the overall 2-sided α of 0.05 will be split between the analyses of the primary endpoints and using 2-sided $\alpha_1 = 0.04$ and the analyses for key secondary endpoint of OS using 2-sided $\alpha_2 = 0.01$.

8.2.3. Primary Analysis and Statistical Inferences for Primary Efficacy Endpoints

8.2.3.1. Statistical Approaches Ensuring Strong Control of Family-wise Type I Error Rate of 2-sided $\alpha_1 = 0.04$

The treatment effect for DSN in Cycle 1-4 and occurrence of SN in Induction will be both tested at the 2-sided 0.04 level based on the primary analysis models specified in Section 8.2.3.2.

8.2.3.2. Primary Analysis for Primary Efficacy Endpoints

Treatment effect on DSN in Cycle 1-4 will be evaluated using nonparametric analysis of covariance (ANCOVA) (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, Region and Prior chemotherapy. 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 1-4 (trilaciclib – placebo), its standard error and 96% CI will be generated and reported from a Satterthwaite t-test and presented.

The treatment effect for occurrence of SN will be evaluated using modified Poisson regression model (Zou 2004). The model will include treatment, Region and Prior chemotherapy as the fixed effect with baseline ANC value as a covariate. The log-transformed number of cycles will be used as the offset in the model to account for the variable duration among patients. The 2-sided p-value, adjusted relative risk (aRR) (trilaciclib vs placebo) and its 96% CI will be generated from the model and reported.

Data listings will include all collected ANC values during Induction, derived DSN in Cycle 1-4, and indicator for occurrence of SN by cycle during Induction.

8.2.4. Primary Analysis and Statistical Inferences for Key Secondary Endpoint - Overall Survival

8.2.4.1. Timing for Overall Survival Analysis

At the time when 157 death events are observed or at 52 months after the date of first randomization, whichever comes first, the study will be concluded, and the final study database will be locked to perform the OS analysis.

8.2.4.2. Statistical Significance Level for Analysis of Overall Survival

As described in Section 8.2.2, a Type I error rate of 2-sided $\alpha_2 = 0.01$ is originally assigned to the analysis for OS with $\alpha_1 = 0.04$ being used for testing treatment effect on the primary endpoints. If the statistically significant treatment effect is established at the 0.04 level for DSN at Cycle 1-4 and occurrence of SN as outlined in Section 8.2.3, $\alpha_1 = 0.04$ will be added onto to $\alpha_2 = 0.01$ to allow a full α of 2-sided 0.05 to test the treatment effect on OS following the fallback procedure (Wiens 2003).

In summary, there are two possible scenarios with respect to statistical significance level when testing treatment effect on OS:

- **Scenario 1:** If one of the tests in the fixed sequence procedure for DSN in Cycle 1-4 and occurrence of SN fails to establish the statistical significance, OS will be tested at 2-sided 0.01 level.
- **Scenario 2:** If the statistical significance for DSN in Cycle 1-4 and occurrence of SN are established at the level of 2-sided 0.04, OS will be tested at 2-sided 0.05 level.

8.2.4.3. Statistical Analysis Models for Overall Survival

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 factors of Region, Prior chemotherapy, and BRAF status. The magnitude of treatment effect, HR (trilaciclib vs. placebo) along with its (1-α) x100% 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% CI 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% CIs (Kalbfleisch, 1980) at selected landmarks of 24, 36, and 48 months for OS.

Data listings will be generated for OS. The duration of total follow-up will be included in the OS data listing along with detailed information supporting the calculation of OS, the censoring indicator, and reasons for censoring.

8.2.5. Estimand Framework and Sensitivity Analysis for Primary and Key Efficacy Endpoints

The complete framework of estimands for the primary and key secondary endpoints following International Council for Harmonisation (ICH) E9 (R1) (2020) are presented in Appendix 2. The identified intercurrent event (ICE) and the strategies for ICE classification with the justifications are also elaborated for each of the estimands in the appendix.

In this section, ICEs and strategies for ICE handling cited from Appendix 2 will be presented for each estimand and the corresponding sensitivity analysis, if warranted, will be described.

8.2.5.1. Estimand Framework and Sensitivity Analysis for DSN in Cycle 1-4

The identified ICEs for one of the primary estimands, DSN in Cycle 1-4, the strategies for the primary analysis (Section 8.2.3) and the strategies for the sensitivity analyses are presented in Table 8.

The justifications for the strategies from primary to sensitivity can be found in Appendix 2.

Table 8: The Intercurrent Events and Handling Strategies for DSN in Cycle 1-4

ICE	Primary	Sensitivity
1. Patients who randomized but not dosed by any study drug	Treatment Policy Strategy	Principal Stratum Strategy
2. Treatment discontinuation prior to any SN in Cycle 1-4	Treatment Policy Strategy	None
3. Receipt of GCSF administration in Cycle 1-4	Treatment Policy Strategy	Hypothetical Strategy

To address the potential impact of ICE 1 and 3 on the treatment effect for this estimand and based on the identified policy for sensitivity analysis, DSN in Cycle 1-4 will be derived using two alternative definitions:

- Not to assign 0 for DSN for those patients who were in the mITT population but did not receive any study drug. These patients will then be automatically excluded from the analysis model.
- Consider the first SN event that occurred after a dose of GCSF was administrated in Cycle 1, 2, 3, or 4 as non-event, and then re-derive the DSN based on rules described in Section 8.1.1.

For the two alternatively derived DSN in Cycle 1-4, the treatment effect will be evaluated using the same statistical model as described in Section 8.2.3.2.

In addition, treatment effect on DSN in Cycle 1-4 will be evaluated after adjusting for the potential impact of GCSF use in the first 4 cycles of Induction. In that analysis, the status of GCSF use in Cycle 1-4 (Yes or No) will be added to the primary analysis model for DSN in Cycle 1-4 as described in Section 8.2.3. Subgroup analysis for DSN in Cycle 1-4 for patients with or without GCSF use in the first 4 cycles of Induction will also be performed (see Section 8.5.1).

8.2.5.2. Estimand Framework and Sensitivity Analysis for Occurrence of SN

The identified ICEs for one of the primary estimands, occurrence of SN, the strategies for the primary analysis (Section 8.2.3) and the strategies for the sensitivity analyses are presented in Table 9.

The justifications for the strategies from primary to sensitivity can be found in Appendix 2.

Table 9: The Intercurrent Events and Handling Strategies for Occurrence of SN

ICE	Primary	Sensitivity
1. Patients who randomized but not dosed by any study drug	Treatment Policy Strategy	Principal Stratum Strategy
2. Treatment discontinuation from Induction prior to any SN	Treatment Policy Strategy	None
3. Receipt of GCSF administration during Induction	Treatment Policy Strategy	Hypothetical Strategy

To address the potential impact of ICE 1 and 3 on the treatment effect for this estimand and based on the identified policy for sensitivity analysis, the following sensitivity analyses will be performed for occurrence of SN.

- Exclude those patients who were in the mITT population but did not receive any study drug from the analysis population, and then evaluate the treatment effect using the modified Poisson model as described in Section 8.2.3.2.
- Re-define the binary variable of occurrence of SN by considering any SN events that occurred after a dose of GCSF administration as "No", and then evaluate the treatment effect using the modified Poisson model as described in Section 8.2.3.2.

In addition, treatment effect on occurrence of SN in Induction will be evaluated after adjusting for the potential impact of GCSF use during Induction. In that analysis, the status of GCSF use in Induction (Yes or No) will be added to the primary analysis model for occurrence of SN in Induction as described in Section 8.2.3. Subgroup analysis for occurrence of SN for patients with or without GCSF use in Induction will also be performed (see Section 8.5.1).

To facilitate the understanding of GCSF administration in Induction and to provide information for the above stated sensitivity analysis, the first occurrence of SN in Induction, in Cycle 1 to Cycle 4, in Cycle 5 to Cycle 8, and in Cycle 9 to Cycle 12 will be tabulated by treatment group. In addition, the first occurrence of SN in Induction will also be tabulated by cycle for each treatment group.

Furthermore, a logistic regression model with the terms of treatment, Prior chemotherapy, Region, baseline ANC values, and log-transformed duration of cycles in Induction as covariate will be used to evaluate treatment effect on occurrence of SN. The odds ratio, its 96% CI and the p-value will be generated and reported. A stratified Cochran-Mantel-Haenszel test with the stratum of Prior chemotherapy and Region will also be used to assess treatment effect on occurrence of SN in Induction. Model-adjusted relative risk, its 96% CI and p-value will be generated and reported.

8.2.5.3. Estimand Framework for OS

The identified ICEs for the key secondary estimand OS along with the corresponding strategies for the primary analysis (Section 8.2.4) are presented in Table 10. The justifications for the strategies from primary analysis and none for sensitivity analysis can be found in Appendix 2.

Table 10: The Intercurrent Events and Handling Strategies for OS

ICE	Primary	Sensitivity
1. Subsequent anticancer therapy	Treatment Policy Strategy	None
2. Study discontinuation including lost-to-follow up	Treatment Policy Strategy	None
3. Curative intent surgical resection	Treatment Policy Strategy	None

8.2.6. Analysis for Secondary Endpoints - Other Myelosuppression Endpoints

Statistical analysis methods for other myelosuppression endpoints derived based on data collected in Induction (Section 8.1.3) are described in this section. Corresponding data listings will be provided.

8.2.6.1. Analysis for Binary Myelosuppression Endpoints

For each binary myelosuppression endpoint as specified in Table 6 in Section 8.1.3, the number and percentage of patients with at least one occurrence during Induction 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 Region and Prior chemotherapy as the fixed effect with corresponding baseline value as a covariate when applicable. The variable duration of Induction among patients will be adjusted by using the log-transformed duration of Induction (in the unit of cycles or weeks) as the offset variable in the model. A 2-sided p-value, aRR (trilaciclib versus placebo) 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 6 in Section 8.1.3) 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 Induction that is used to construct an offset variable in the model is the number of cycles in Induction 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 Induction that is the same as the duration of study drug exposure in Induction (defined in Table 3, Section 4.3) will be used as the duration variable.

Additionally, the proportion of patients with Grade 3 or 4 neutropenia in Cycles 1 – 4, Cycles 5 – 8, and Cycles 9 – 12 will be tabulated by treatment group.

8.2.6.2. Analysis for Counting Myelosuppression Endpoints

For the counting myelosuppression endpoints as specified in Table 6 (Section 8.1.3), the total number of the events, the duration of Induction (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 two factors of Region and Prior chemotherapy as the fixed effect with 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 Induction as the offset variable in the model. A 2-sided p-value, aRR (trilaciclib versus placebo) 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 6 in Section 8.1.3) 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 Induction (used to calculate the raw event rate and to construct an offset variable in the model) is the number of cycles in Induction for the endpoints of number of GCSF administrations and number of dose reductions, and it is the number of weeks in Induction 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 Induction (the same as the duration of study drug exposure in Induction) is defined in Table 3 (Section 4.3).

8.2.7. Analysis for Secondary Endpoints - Healthcare Utilization Endpoints

For the binary healthcare utilization endpoints (occurrence of hospitalizations due to any cause, occurrence of hospitalizations due to CIM, occurrence of hospitalizations due to sepsis or serious infections, and occurrence of IV antibiotic administration), the number and percentage of patients with at least one occurrence during Induction 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 Region and Prior chemotherapy as the fixed effect. The variable duration of Induction among patients will be adjusted by using the log-transformed cycles as the offset variable in the model. A 2-sided p-value, aRR (trilaciclib versus placebo) and its 95% CI will be generated from the modified Poisson regression model.

For the counting endpoint, number of hospitalizations due to CIM, the total number of events, the total number of cycles in Induction, and raw event rate per 100 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 two factors of Region and Prior chemotherapy as the fixed effect. The variable duration of Induction among patients will be adjusted by using the log-transformed number of cycles as the offset variable in the model. A 2-sided p-value, aRR (trilaciclib versus placebo) and its 95% CI will be generated from the negative binomial model.

Corresponding data listings will be provided.

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

8.2.8.1. Analysis for Secondary Endpoint - Progression Free Survival

PFS analysis will be performed twice in this study. The first time is around the time point of 35 months post first randomization and the second time at the end of the study.

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 factors of Region, Prior chemotherapy, and BRAF status. The magnitude of treatment effect, HR (trilaciclib vs. placebo) along with its (1-α) x100% 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% CI calculated based on the method by Brookmeyer and Crowley (1982).

Data listings will be generated. Tumor scan data will be included in the PFS data listing. The detailed information supporting the calculation of PFS along with the censoring indicator, and reasons for censoring will also be included.

8.2.8.2. Analysis for Secondary Endpoints - Tumor Response and Duration of Objective Response

The analysis for BOR and ORR (see variable definitions in Section 8.1.5) will be based on the RE population.

Tumor response status classified by BOR will be tabulated by treatment group with the number and percentage of patients in each category of CR, PR, stable disease (SD), PD, or not evaluable (NE), where the percentages are calculated based on the number of patients in the RE population for the respective group.

ORR along with its exact 95% two-sided CI using the Clopper-Pearson method will be computed for each treatment group. The treatment effect on ORR will be evaluated using a Cochran–Mantel–Haenszel (CMH) test accounting for the factors of Region, Prior chemotherapy and BRAF status. The adjusted proportion difference (trilaciclib vs placebo) and its 95% CI will be calculated using CMH weight (as described in Kim, 2013).

Confirmed ORR will be summarized and analyzed using the same methods as are used for the ORR.

For patients who achieved confirmed CR or PR as BOR status, DOR will be calculated and 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).

Data listings will include tumor scan data, Investigator determined timepoint responses and BOR, programmatically derived tumor response status, and confirmed tumor response status.

8.2.9. Exploratory Analysis - Anti-tumor Endpoints by CDK4/6 Biomarker Signature

Analyses described in this section will be performed at the time of final analysis.

The distribution of CDK4/6 signature by treatment group will be tabulated for the mITT population. A Chi-square test will be used to assess the difference in distribution of patients' CDK4/6 signature status (i.e., CDK4/6 independent, CDK4/6 dependent, and CDK4/6 indeterminate) between the two treatment groups.

Anti-tumor endpoints (ORR, PFS, and OS) will be evaluated by subgroup of patients with different CDK 4/6 signature status in the mITT population. Within each type of signature, treatment group difference in ORR and its 95% CI will be generated using the same methods as described in Section 8.2.8. The treatment effect for PFS (or OS) will be estimated by a hazard ratio (HR) and its 95% CI generated from a Cox proportional hazard model with the same terms as described in Section 8.2.4.3.

Data listings include CDK 4/6 signature status and above-mentioned anti-tumor endpoints.

8.2.10. Exploratory Analysis - Myelosuppression Endpoints during Overall Treatment Period

The overall treatment period includes Induction and Maintenance (Section 4.3) with fluorouracil, leucovorin, and bevacizumab continued from Induction to Maintenance.

Definitions for occurrence of SN and other myelosuppression endpoints as described in Table 6 in Section 8.1.3 can all be extended to include data collected up to the end of last cycle in Maintenance. Similarity, such extension of definition can be made to healthcare utilization endpoints (Section 8.1.4).

Myelosuppression endpoints and healthcare utilization endpoints during the overall treatment period will be summarized with appropriate summary statistics by treatment group. Treatment group difference for each of these endpoints will be quantified by a point estimate and its 95% CI using the similar model as outlined in Section 8.2.6 and Section 8.2.7. No testing of treatment group difference will be conducted.

Corresponding data listings will be provided.

8.3. Handling of Missing Data

Since all scheduled and unscheduled laboratory assessments will be included in deriving myelosuppression endpoints (Section 8.1.1 and Section 8.1.3) and the patients must have demonstrated the following before continuing the study treatment from one cycle to the next: ANC < 1.0 x 10^9/L, Hgb <8.0 g/dL, or platelets < 50.0 x 10^9/L based on the CTCAE toxicity criteria. As such, the potential risk of missing complete blood count (CBC) data collection to derive the primary endpoints and other myelosuppression endpoints is at minimum.

Missing data impact on other endpoints are in general managed by derivation rules (Section 8.1).

8.4. Efficacy Endpoints to Analyzed on Per-protocol Population

The definition for the PP population is provided in Section 3.3.

Since the treatment effect on the primary efficacy endpoints along with other neutrophil-related endpoints (Table 11) can be relatively more easily impacted by inappropriate use of supportive care, like GCSF, these endpoints will be analyzed in PP population using the same statistical models as described in Section 8.2.3.2 and Section 8.2.8.

Table 11: Endpoints to be Analyzed in the Per-protocol Population

Lineage	Endpoint
Neutrophils	DSN in Cycle 1-4
	Occurrence of severe neutropenia
	Occurrence of GCSF administration
	Number of GCSF administrations (event rate per 100 cycle)
	Occurrence of Grade 3 or 4 neutropenia

DSN=duration of severe neutropenia; GCSF=granulocyte colony stimulating factor

8.5. Subgroup Analysis

Subgroup analysis for the primary efficacy endpoints will be performed in the first planned analysis, whereas subgroup analysis for PFS and OS will be conducted when PFS and OS are analyzed, respectively.

8.5.1. Subgroup Analysis for DSN in Cycle 1-4 and Occurrence of SN in Induction

DSN in Cycle 1-4 and occurrence of SN in Induction will be the dependent variables to perform the subgroup analysis for each of the following subgroups:

1. Age group (< 65 or ≥ 65)
2. Gender (male or female)
3. Region (US, Eastern Europe, Western Europe, and China)
4. Prior chemotherapy (yes or no)
5. GCSF administration (see below for different definitions of this subgroup for DSN in Cycle 1-4 and occurrence of SN)

DSN at Cycle 1-4 and occurrence of SN in Induction will be tabulated within each stratum of a subgroup by treatment group. Within each stratum of each subgroup, the group mean difference for DSN in Cycle 1-4 will be generated from a Satterthwaite t-test along with its SE and 95% CI.

Within each stratum of Age and Gender, the aRR and its 95% CI for occurrence of SN in Induction will be generated using a modified Poisson model as outlined in Section 8.2.3. The treatment-by-subgroup interaction will be tested by a different modified Poisson model with additional terms of subgroup and treatment-by-subgroup interaction. Statistically significant interaction is judged by an interaction p-value that is < 0.20.

To generate aRR and its 95% CI for occurrence of SN with the stratum of subgroup Region or Prior chemotherapy, the same factor will be eliminated from the modified Poisson model. There will be no treatment-by-subgroup interaction testing for these two subgroups since they were

either created from a randomization stratification factor or were chosen as a randomization stratification factor.

GCSF use in the first 4 cycles of Induction (Yes or No) will be used as the subgroup to perform the subgroup analysis for DSN in Cycle 1-4, while GCSF in Induction (Yes or No) will be used as the subgroup to perform the analysis for occurrence of SN.

Subgroup analysis results across all subgroups will be graphically displayed by forest plot for DSN in Cycle 1-4 and occurrence of SN, respectively. For DSN at Cycle 1-4, the mean difference in DSN and its 95% CI for each stratum of a subgroup will be displayed; for occurrence of SN, the aRR and its 95% CI for each stratum of a subgroup will be displayed.

8.5.2. Subgroup Analysis for PFS and OS

The following subgroups have been identified to assess whether treatment effect on PFS and OS, respectively, are 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, Eastern Europe, Western Europe, and China)
5. Prior chemotherapy (yes or no)
6. BRAF status (yes or no)

Within each stratum of Age, Gender, Race, and ECOG, a Cox proportional hazard model with the terms of treatment, Region, Prior chemotherapy and BRAF status will be used to estimate the HR (trilaciclib over placebo) and its 95% CI for PFS and OS, respectively. Treatment-by-subgroup interaction will be tested by a different Cox model with additional terms of the subgroup and the treatment-by-subgroup interaction. Statistically significant interaction is judged by an interaction p-value that is < 0.20.

To generate the HR and its 95% CI within each stratum for the subgroup Region, Prior chemotherapy or BRAF status, 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 three were either chosen as randomization stratification factors or obtained from a randomization stratification factor because of the anticipated impact on the outcome of PFS or OS.

A forest plot for HR and its 95% CI across all subgroups will be produced for PFS and OS, respectively.

In addition, the number and percentage of patients who died among those patients who underwent curative intent surgical resection during the study will be summarized. If the number of patients who underwent curative intent surgical resection is sufficient to allow the application of a Cox proportional regression model, the HR and its 95% CI for OS will be generated from a Cox regression model with the term of treatment.

9. SAFETY ANALYSIS

9.1. General Consideration of Safety Analysis

Safety data summaries will be on based the Safety Population as defined in Section 3.4 of this SAP.

Unless otherwise specified, all safety data collected in Induction (i.e., from Day 1 of Cycle 1 in Induction to the end of last cycle in Induction) will be summarized in the first planned analysis. At the time of 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 "during the analysis period" refers to the respective analysis period of interest (i.e., the first planned analysis or the final analysis). All safety data collected through scheduled or non-scheduled visits during the analysis period will be included in the safety data analyses.

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.

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. All AEs are reported since the first dose of any study drug until 30 days after the last dose of study drug. 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 24.1. The severity (toxicity grades 1-5) of AEs will be graded according to the NCI CTCAE version 5.0 by the Investigator.

Hematologic Adverse Events

AEs related to hematologic toxicity will be collapsed based on the PTs from MedDRA version 24.1 and will be summarized separately (see Section 9.2.3). Table 12 outlines those PTs that will be collapsed.

Table 12: Hematologic Preferred Terms to be Collapsed

Term presented in the Output	Preferred Term
Neutropenia	Neutropenia
	Neutrophil count decreased
Anemia	Anemia
	Anaemia
	Red blood cell count decreased
	Hemoglobin decreased
Thrombocytopenia	Thrombocytopenia
	Platelet count decreased
Lymphocytopenia	Lymphocytopenia
	Lymphopenia
	Lymphocyte count decreased
Leukopenia	Leukopenia
	White blood cell count decreased

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 6 categories:

- Phlebitis/Thrombophlebitis
- Injection site reaction
- 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 PTV will be used; if PTV 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, the SOC and PT within a SOC will be presented in descending order based on the incidence from all patients. 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/placebo, and to each other study drug), and AESI for trilaciclib/placebo.

At the time of performing final analysis, in addition to generating the overall AE summary table for the data collected during entire the entire treatment period, an overall AE summary table will also be generated for the AEs collected during Maintenance. That is, AEs reported after the first dose in Cycle 1 of Maintenance to the end of last cycle in Maintenance (Table 3 in Section 4.3).

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 SOC and PT
4. AEs leading to discontinuation of any study drug
5. AEs leading to death
6. AEs related to any and each study drug
7. Hematological AEs by collapsed PT and CTCAE grade
8. Serious AEs
9. Serious AEs related to any and each study drug
10. AESI for trilaciclib will be summarized.

In the above, hematological AEs will be reported as they are with the exception of item 7 (Hematological AEs by collapsed PT and CTCAE grade), for which the collapsed terms as specified in Table 12 (Section 9.2.1) will be reported by the descending order of frequency based on the overall group.

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 onset or stop, grade and causality for each AE. AESI for trilaciclib/placebo 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 13 will be measured according to Schedule of Assessments in Appendix 1.

Table 13: 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.

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) < 2x ULN, and total bilirubin ≥ 2x ULN
- 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 parameter in the clinical chemistry and hematology laboratory group, respectively, 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.

In addition, shift in CTCAE grade from baseline to the worst post-baseline value during treatment period will be produced for each treatment group. The shift tables will include patients who had non-missing baseline and at least one non-missing post-baseline value for the parameter of interest.

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 group of chemistry, hematology, and urinalysis. In addition, coagulate laboratory parameters as collected for some patients as part of the entry criteria will also be presented in the data listing. 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.

Baseline vital signs refers to the measurements taken at the Screening visit. 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 who had 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 14.

Table 14: 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

The 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, change from baseline at each post-first dose assessment, 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.

A shift table that tabulates ECOG status at baseline and the worst status post first dose of any study drug during the treatment period will be generated for each treatment group. Patients missing baseline or without any post baseline ECOG score will be excluded from the analysis.

All ECOG data will be included in a data listing.

9.6. 12-lead Electrocardiograms

9.6.1. Electrocardiograms Parameters

The standard 12-lead Electrocardiogram (ECG) will collect heart rate, PR interval, QRS interval, RR interval, and QT interval at the frequency according to Schedule of Assessments in Appendix 1. Investigator's clinical interpretation of 12-lead ECG results by normal or abnormal will also be collected.

Since either QTcF or QTcB could be collected by different study sites, QTcF (using Fridericia's method) will be calculated from the QT and RR (converted from collected ms to sec) intervals based on the formula:

QTcF = Uncorrected QT/ (RR Interval)^1/3, if QT and/or RR are missing, the QTcF will be left as missing.

Change from baseline to the highest/lowest value across all post-baseline measurements for QTcF will be calculated. Patients with who had a non-missing baseline and at least one non-missing measurement post-first dose will be included in the calculation.

The potentially clinically significant ECG findings are defined by the highest/lowest value across all post-baseline assessments while during the treatment period for all parameters except for QTcF, for which both observed values and change scores are used to define the PCS findings (Table 15). For QTcF, a total of 5 different criteria are defined with some of these are mutually exclusive and some cumulative (denoted by Criterion Index in Table 15).

Table 15: Criteria for Potentially Clinically Significant ECG Findings

ECG Parameter	Direction or Criterion Index	Highest/Lowest Observed Value	Change from Baseline to the Highest/Lowest Observed Value
RR Interval	High	> 1200 ms	--
	Low	< 500 ms	--
PR Interval	High	≥ 210 ms	--
QRS Interval	High	≥ 120 ms	--
	Low	≤ 50 ms	--
QT Interval	High	≥ 500 ms	--
	Low	≤ 300 ms	--
QTcF	Index 1 (mutually exclusive)	≥ 500 msec	--
		≥ 480 and < 500 msec	--
		≥ 450 and < 480 msec	--
		≤ 300 msec	--
	Index 2	≥ 480 msec	--
	Index 3	≥ 450 msec	--
	Index 4 (mutually exclusive)	--	Increase ≥ 60
		--	Increase ≥ 30 and < 60 ms
	Index 5	--	Increase ≥ 30 ms

9.6.2. Analysis for Electrocardiograms Parameters

For each ECG parameter in Table 15, the number and percentage of patients who met each potentially clinically significant criterion will be summarized by treatment group.

Investigator's clinical interpretation of the 12-lead ECG results (normal or abnormal) will be tabulated to present shift from baseline to the worst case post-dose during the treatment period by treatment group. Similarly, a shift table from baseline to the last post-baseline assessment during the treatment period will be generated for each treatment group.

All ECG parameters as collected along with corrected values of QTcF will be included in the data listing. In the listing, the flag of meeting a PCS criterion and the flag indicating investigator's determined abnormality are also included.

10. CHANGES FROM THE PROTOCOL

- In the protocol Section 5, it stated that occurrence and number of events will be evaluated for each of the secondary myelosuppression endpoints. Several of these endpoints are expected to have low repeated counts or the summaries of number of events are expected to be non-informative, therefore, the following endpoints will only be analyzed for occurrence but not for the number of events:

  Febrile neutropenia AEs, Grade 3 or 4 decreased hemoglobin laboratory values, ESA administration, Grade 3 or 4 decreased platelet count laboratory values, Grade 3 or 4 hematologic lab values, number of all-cause hospitalizations, oral or oral + IV antibiotic use.

- In the SAP, an additional endpoint of Grade 3 or 4 neutropenia derived from the laboratory parameter ANC has been added to evaluate the extent of clinically relevant neutropenia more fully. While Grade 4 neutropenia during Induction and the duration of Grade 4 neutropenia in Cycle 1-4 are used as the primary endpoints, both Grade 3 and Grade 4 neutropenia are important attributors to dose reductions, cycle delays, and subsequent use of prophylactic GCSF. Therefore, it is believed that evaluating treatment effect on this endpoint will be clinically meaningful.

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12. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Table 16: Schedule of Assessments: Screening and Induction Cycle 1

Assessment	**Screening**	**Rand.**	**Induction Cycle 1 (14-day cycle)**						
Day	**-28 to -1**	**-3 to -1[a]**	**1**	**2**	**4 (±1 day)**	**6 (±1 day)**	**8 (±1 day)**	**10 (±1 day)**	**12 (±1 day)**
Informed Consent	X								
Demographics	X								
Medical History and CRC History[b]	X								
MMR/MSS and BRAF V600E status[c]	X								
Eligibility Evaluation and Randomization	X	X							
G8 Health Status Screening Tool (Patients > 70yrs only)	X								
Archived tumor sample	X								
ECOG Performance Status	X		X						
Physical Exam[d]	X		X						
Height, Weight	X[e]		X						
Vital Signs	X		X[f]						
12-lead Electrocardiogram	X[g]		X[g]	X[g]					
Clinical Chemistry	X		X[h]						
Hematology	X		X[i]	X	X	X	X	X	X
INR/aPTT	X								
Urinalysis (dipstick)	X		X						
Pregnancy test (WOCBP)[j]		X							

Assessment	Screening	Rand.	Induction Cycle 1 (14-day cycle)						
Day	-28 to -1	-3 to -1[a]	1	2	4 (±1 day)	6 (±1 day)	8 (±1 day)	10 (±1 day)	12 (±1 day)
Tumor Assessment by RECIST v1.1[k]	X								
Trilaciclib or Placebo[l]			X	X					
Irinotecan			X						
Oxaliplatin			X						
Leucovorin			X						
Fluorouracil			X	X					
Bevacizumab			X						
FACT-An (includes FACIT-F), FACT-C, PGIS, and PGIC[m]			X				X		
EQ-5D-5L			X				X		
Blood sample for PK[n]			X	X					
Blood sample for Immunologic and Hematologic Markers			X						
AEs			X						
Concomitant Medications	X[b]	X[b]	X						

AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=beta human chorionic gonadotropin; CRC=colorectal cancer; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=5-level EQ-5D; FACT-An=Functional Assessment of Cancer Therapy – Anemia; FACIT-F=Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-C=Functional Assessment of Cancer Therapy – Colorectal; FACT-G=Functional Assessment of Cancer Therapy – General; INR=international normalized ratio; IWRS=interactive web response system; MMR=mismatch repair; MRI=magnetic resonance imagining; MSI=microsatellite instable; PE=physical exam; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; pMMR/MSS=proficient mismatch repair/microsatellite stable; RECIST=Response Evaluation Criteria in Solid Tumors; yrs=years; WOCBP=women of childbearing potential.

[a] Patients can be randomized and receive Cycle 1 Day 1 on the same day. When required by institutional procedures, randomization will be allowed up to 7 days prior to dosing without a protocol deviation. Screening procedures must be completed prior to randomization and the screening window remains 28 days.

[b] Including medical and surgical history, documentation of CRC diagnosis and prior CRC therapy, and prior medications (current and those taken within 14 days of informed consent).

[c] Documentation of BRAF V600E and pMMR/MSS is required; patients with deficient MMR/MSI-high or MSI-low CRC are not eligible for this study. If historical pMMR/MSS and/or BRAF V600E mutational status are not known, a tumor specimen (archival or fresh biopsy) must be sent for testing and results must be available at the time of randomization in IWRS. If testing cannot be completed using a standard clinical assay performed institutionally/locally, the tumor specimen may be sent to the Sponsor's designated central laboratory for analysis. If institutional/local testing is unavailable, please contact your CRA.

[d] Full PE at Screening, brief PE at all other timepoints.

[e] Height measured only at Screening; weight measured at Screening and Day 1 of each cycle in Induction and Maintenance.

[f] Vitals (BP, HR, temperature) should be taken 15 minutes (± 10 minutes) before and after the trilaciclib/placebo infusion.

[g] Perform triplicate ECGs at screening and on Day 1 of Cycle 1 at the following timepoints: predose (trilaciclib/placebo) at any time prior to dosing, within 30 minutes following the end of the trilaciclib/placebo infusion, and at 3 hours after the start of trilaciclib/placebo infusion (± 30 minutes). Triplicate ECGs should also be performed on Day 2 of Cycle 1 at the following timepoints: predose (trilaciclib/placebo) at any time prior to dosing and within 30 minutes following the end of the trilaciclib/placebo infusion. Additional ECGs during the study may be performed as clinically indicated. Any ECG with a QTc value of > 500 or any other clinically significant abnormal finding should be repeated every 5 minutes for a total of three ECGs to confirm this finding, if not already recorded in triplicate.

[h] Clinical chemistry and urinalysis may be obtained up to 3 calendar days prior to dosing.

[i] Hematology may be obtained up to 1 calendar day prior to dosing.

[j] Female patients of childbearing potential: serum β-hCG at enrolment (eg, signed consent and during window allowing randomization in IWRS; results should be available prior to randomization).

[k] Initial staging should include, at a minimum, CT or MRI of chest, abdomen and pelvis. IV contrast should be used unless contraindicated. Oral contrast can be used at the Investigator's discretion.

[l] Trilaciclib or placebo will be administered as a 30-minute IV infusion prior to FOLFOXIRI/bevacizumab chemotherapy on Day 1 and on Day 2 of every cycle. Chemotherapy cannot be administered until after completion of the trilaciclib or placebo infusion on Day 1. The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on Day 1 should not be greater than 4 hours. The second dose of trilaciclib/placebo should be administered on Day 2. Trilaciclib or placebo will only be administered if chemotherapy is also to be administered on that day.

[m] FACT-An, FACT-C, PGIS, and EQ-5D-5L will be administered on Days 1 and 8 of Cycle 1. PGIC will only be administered on Day 8 of Cycle 1. FACIT-F is embedded within the FACT-An. Patient-reported outcome questionnaires may be administered up to 1 calendar day prior to the first dose of each cycle; questionnaires administered on Day 8 may be obtained ±1 day of scheduled visit; **NOTE**: questionnaires should be completed on the same day blood sample is collected for hematology assessment. Questionnaires must be completed prior to the administration of any study drug and should be administered prior to the conduct of any study procedures at that visit.

[n] Four blood samples for PK analysis of trilaciclib and any metabolites will be collected: on Cycle 1 Day 1 at the end of trilaciclib/placebo infusion (within 5 minutes prior to the end of the infusion), and at 25 to 45 minutes and 4-6 hours post the end of the trilaciclib/placebo infusion, as well as predose (trilaciclib/placebo) on Cycle 1 Day 2. Three samples will be collected for PK analysis of irinotecan and its metabolite (SN-38): on Cycle 1 Day 1 at the end of irinotecan infusion (within 5 minutes prior to the end of the infusion) and at 4-6 hours post the end of the irinotecan infusion as well as predose (trilaciclib/placebo) on Cycle 1 Day 2.

Table 17: Schedule of Assessments: Induction (Cycles 2-12), Maintenance, and Survival Follow-up

Assessment	**Induction (14-day cycles) [Maximum 12 cycles]**			**Last Induction Cycle only if no Maintenance**	**Maintenance (14-day cycles)**		**Post Treatment Visit**	**Survival Follow Up**
Day	**1**	**2**	**8 (±1 day)**	**15 (±1 day)**	**1**	**2**	**30 ±7d post last dose**	
ECOG Performance Status	X				X		X	
Physical Exam (Odd cycles only in both Induction and Maintenance, eg, C1, 3, 5, etc)	X				X		X	
Weight	X				X		X	
Vital Signs[a]	X				X		X	
12-lead Electrocardiogram	X[b] [C2 only]	X[b] [C2 only]						
Clinical Chemistry[c]	X				X		X	
Hematology[d]	X		X [C2-4 only]	X	X		X	
INR/aPTT (as clinically indicated during the study)								
Urinalysis[c] (dipstick)	X				X			
Pregnancy test (WOCBP, q month)[e]	X				X		X	
Tumor Assessment by RECIST v1.1	X[f] (q8 weeks regardless of dosing)				X[f] (q12 weeks)		X[g]	X[g]
Trilaciclib or placebo[h]	X	X			X	X		
Irinotecan	X							
Oxaliplatin	X							

Assessment	**Induction (14-day cycles) [Maximum 12 cycles]**			**Last Induction Cycle only if no Maintenance**	**Maintenance (14-day cycles)**		**Post Treatment Visit**	**Survival Follow Up**
Day	**1**	**2**	**8 (±1 day)**	**15 (±1 day)**	**1**	**2**	**30 ±7d post last dose**	
Leucovorin	X				X			
Fluorouracil	X	X			X	X		
Bevacizumab	X				X			
FACT-An (includes FACIT-F), FACT-C, PGIS, PGIC[i]	X		X [C2-4 only]	X[j]	X		X	
EQ-5D-5L	X		X [C2-4 only]	X[j]	X		X	
Blood sample for Immunologic and Hematologic Markers	X [C2, C5, only]				X [C1 only]			
AEs	X							
Concomitant Medications	X							
Survival Follow-up Contact (every other month)								X[k]

AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=beta human chorionic gonadotropin; C=cycle; ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=5-level EQ-5D; FACT-An=Functional Assessment of Cancer Therapy – Anemia; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-C=Functional Assessment of Cancer Therapy – Colorectal; FACT-G=Functional Assessment of Cancer Therapy – General; INR=international normalized ratio; IWRS=interactive web response system; PE=physical exam; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; RECIST=Response Evaluation Criteria in Solid Tumors; WOCBP=women of childbearing potential.

[a] Vitals (blood pressure, heart rate, temperature) should be taken 15 minutes (± 10 minutes) before and after the trilaciclib/placebo infusion.

[b] Perform triplicate ECGs on Day 1 of Cycle 2 at the following timepoints: predose (trilaciclib/placebo) at any time prior to dosing, within 30 minutes following the end of the trilaciclib/placebo infusion, and 3 hours after the start of trilaciclib/placebo infusion (± 30 minutes). Triplicate ECGs should also be performed on Day 2 of Cycle 2 at the following timepoints: predose (trilaciclib/placebo) at any time prior to dosing and within 30 minutes of the end of the trilaciclib/placebo infusion. Additional ECGs during the study may be performed as clinically indicated. Any ECG with a QTc value of > 500 or any other clinically significant abnormal finding should be repeated every 5 minutes for a total of three ECGs to confirm this finding, if not already recorded in triplicate.

[c] Clinical chemistry and urinalysis may be obtained up to 3 calendar days prior to dosing.

[d] Hematology may be obtained up to 1 calendar day prior to dosing. If the initiation of the next cycle is delayed due to an AE, the patient should have (at least) weekly visits, including CBCs if the AE is hematologic, to follow the AE. Clinical laboratory assessments should be completed on the scheduled Day 1 as well as on the actual first dosing day of that delayed cycle.

[e] Female patients of childbearing potential: serum or urine pregnancy testing every 2nd cycle (e.g., every month) during treatment (Induction and Maintenance) and at the post-treatment visit.

[f] Tumor assessments of chest, abdomen, and pelvis using the same imaging modality as at baseline should be performed every 8 weeks ± 7 days during Induction and every 12 weeks ± 14 days during Maintenance. IV contrast should be used unless contraindicated. Oral contrast can be used at the Investigator's discretion. Timing of scans should be regardless of dosing (e.g., from date of first dose). Additional scans may be performed during the study if clinically indicated.

[g] Perform tumor assessments at the Post Treatment Visit (30 +7d after last dose of study drug) only for patients who have not progressed at the time of study drug discontinuation. For those patients being followed for survival who have not progressed at the time of study drug discontinuation, tumor assessments will be repeated every 12 weeks ± 14 days until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anti-cancer therapy, or study completion. Tumor assessments of chest, abdomen, and pelvis using the same imaging modality as at baseline should be performed. IV contrast should be used unless contraindicated; oral contrast can be used at the Investigator's discretion.

[h] Trilaciclib or placebo will be administered as a 30-minute IV infusion prior to chemotherapy on Day 1 and on Day 2 of every cycle during Induction and Maintenance. Chemotherapy cannot be administered until after completion of the trilaciclib or placebo infusion on Day 1. The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on Day 1 should not be greater than 4 hours. The second dose of trilaciclib/placebo should be administered on Day 2. Trilaciclib or placebo will only be administered if chemotherapy is also to be administered on that day.

[i] FACIT-F is embedded in the FACT-An. Patient reported outcome questionnaires should be completed at the following timepoints: Induction Cycles 2 to 4 (Days 1 and 8), Induction Cycles 5-12 (Day 1), Day 1 of each cycle in Maintenance, and at the post-treatment visit. If a cycle is delayed, the patient should still complete the questionnaires on the scheduled Day 1 of that cycle, as well as the actual first dosing day of that cycle. PRO questionnaires may be administered up to 1 calendar day prior to the first dose of each cycle; questionnaires administered on Day 8 may be obtained ±1 day of scheduled visit. **NOTE**: questionnaires should be completed on the same day blood sample is collected for hematology assessment. Questionnaires must be completed prior to the administration of any study drug and should be administered prior to conduct of any study procedure at that visit.

[j] Administer PRO questionnaires on Day 15 of last induction cycle only if patient does not continue with Maintenance therapy. When patient does not continue in Maintenance, questionnaires do not need to be repeated at both Post Treatment Visit and Day 15 of last induction cycle if < 3 weeks between these 2 timepoints.

[k] If a patient withdraws consent for further study treatment and/or procedures, the site should clarify if the patient remains open to survival contact and associated data collection. See Section 11.12 of the protocol for details of information to be collected during Survival Follow-up.

APPENDIX 2. ESTIMANDS FRAMEWORK FOR PRIMARY AND KEY SECONDARY ENDPOINTS FOR STUDY G1T28-207

In this document, the primary and key secondary endpoints defined in the protocol are described in the estimand framework following ICH E9 (R1) (2020). The strategies for ICE classification in the primary and sensitivity settings are also elaborated for each of the estimands.

Primary Estimands

To assess the myeloprotective effect of trilaciclib on the neutrophil lineage compared with placebo.

DSN in Cycle 1-4

Population:	The mITT population as defined in Section 3.1
Treatment:	Trilaciclib versus placebo administered prior to FOLFOXIRI/bevacizumab
Variable:	See Section 8.1.1
Summary measure:	Treatment difference from the nonparametric ANCOVA model (see Section 8.2.3.2)

Occurrence of SN during Induction

Population:	The mITT population
Treatment:	Trilaciclib versus placebo administered prior to FOLFOXIRI/bevacizumab
Variable:	See Section 8.1.1
Summary measure:	The adjusted relative risk from the modified Poisson model (see Section 8.2.3.2)

Handling of Intercurrent Events for Primary Estimands

DSN in Cycle 1-4

The following ICEs were identified:

- Patients who were randomized but not dosed with any study drug
- Treatment discontinuation in Cycle 1-4
- Receipt of GCSF administration in Cycle 1-4

The following strategies will be used for each of the above ICEs:

ICE	Primary	Sensitivity
1. Patients who were randomized but not dosed with any study drug	Treatment Policy Strategy	Principal Stratum Strategy
2. Treatment discontinuation prior to any SN in Cycle1-4	Treatment Policy Strategy	None
3. Receipt of GCSF administration in Cycle 1-4	Treatment Policy Strategy	Hypothetical Strategy

Justification for Primary and Sensitivity Strategies of ICE

1. Patients who were randomized but not dosed with any study drug

As DSN in Cycle 1-4 was designed as one of the primary endpoint to assess the myeloprotective effect of trilaciclib on the neutrophil lineage compared with placebo, if a patient does not take any study drug, that implies that the patient was discontinued from study between the time of randomization and entering the first cycle of treatment in Induction, and thus there was no neutrophil count data collection for the patient. However, following the ITT principle to include this type of patients in the analysis, a value of 0 for DSN in Cycle 1-4 was assigned to these patients (Section 8.1.1). In this approach, the treatment policy strategy was used (i.e., the occurrence of the ICE was ignored). The impact of this ICE on the analysis outcome is that the number of such patients might not be balanced between two treatment groups, thus, assigning a value of 0 to DSN in Cycle 1-4 could introduce bias to the results. To account for the impact of this ICE to the evaluation of treatment effect on DSN in Cycle1-4, the principal stratum strategy will be used as a sensitivity analysis, in which patients who were randomized but not dosed with any study drug will be excluded from the analysis for DSN in Cycle 1-4.

2. Treatment discontinuation prior to any SN in Cycle 1-4

Treatment discontinuation prior to any SN in Cycle 1-4 may potentially prevent SN from being reported. The treatment policy strategy (i.e., the occurrence of the ICE was ignored) will be used for this ICE in the primary analysis of DSN in Cycle 1-4. However, there is no rational way to predict if the patient may or may not develop SN after treatment discontinuation; therefore, no sensitivity analysis will be performed for this ICE.

3. Receipt of GCSF administration in Cycle 1-4

The treatment policy strategy (i.e., the occurrence of the ICE was ignored) will be used for this ICE in the primary analysis of DSN in Cycle 1-4. Despite that primary prophylactic GCSF will be prohibited in Cycle 1, therapeutic GCSF (administered in response to a neutropenic event) in Cycle 1 and secondary prophylactic GCSF beginning in Cycle 2 and for all subsequent cycles (i.e., after a precipitating event in a prior cycle of therapy) will be allowed per growth factor/neutropenia management guidelines and physician discretion. This GCSF use would potentially boost the neutrophil counts and thus prevent SN from occurring. The imbalance of GCSF use between the treatment group may potentially bias the between-treatment comparison

of DSN. Therefore, the hypothetical strategy (data after ICE will not be used) will be used for a sensitivity analysis.

Occurrence of SN during Induction

The following ICEs were identified:

- Patients who were randomized but not dosed with any study drug
- Treatment discontinuation from Induction
- Receipt of GCSF administration during Induction

The following strategies will be used for each of the above ICEs:

ICE	Primary	Sensitivity
1. Patients who were randomized but not dosed with any study drug	Treatment Policy Strategy	Principal Stratum Strategy
2. Treatment discontinuation from Induction prior to any SN	Treatment Policy Strategy	None
3. Receipt of GCSF administration during Induction	Treatment Policy Strategy	Hypothetical Strategy

Justification for Primary and Sensitivity Strategies of ICE

1. **Patients who were randomized but not dosed with any study drug**

As the occurrence of SN during Induction was designed as one of the primary endpoint to assess the myeloprotective effect of trilaciclib on the neutrophil lineage compared with placebo, if a patient does not take any study drug, that implies that the patient was discontinued from study between the time of randomization and entering the first cycle of treatment in Induction, and thus there was no neutrophil count data collection for the patient. However, following the ITT principle to include this type of patients in the analysis, a value of 0 for the occurrence of SN during Induction was assigned to these patients (Section 8.1.1). In this approach, the treatment policy strategy was used (i.e., the occurrence of the ICE was ignored). The impact of this ICE on the analysis outcome is that the number of such patients might not be balanced between two treatment groups, thus, assigning a value 0 to the occurrence of severe neutropenia during Induction could introduce bias to the results. To account for the impact of this ICE to the evaluation of treatment effect on the occurrence of SN during Induction, the principal stratum strategy will be used as sensitivity analysis, in which patients who were randomized but not dosed with any study drug will be excluded from the analysis for the occurrence of SN during Induction.

2. **Treatment discontinuation from Induction prior to any SN**

Treatment discontinuation from Induction prior to any SN may potentially prevent SN from being reported. The treatment policy strategy (i.e., the occurrence of the ICE was ignored) will be used for this ICE in the primary analysis of the occurrence of SN during Induction. However, there is no rational way to predict if the patient may or may not develop SN after treatment discontinuation; therefore, no sensitivity analysis will be performed for this ICE.

3. **Receipt of GCSF administration during induction**

The treatment policy strategy (i.e., the occurrence of the ICE was ignored) will be used for this ICE in the primary analysis of the occurrence of severe neutropenia during Induction. Despite that primary prophylactic GCSF will be prohibited in Cycle 1, therapeutic GCSF (administered in response to a neutropenic event) in Cycle 1 and secondary prophylactic GCSF beginning in Cycle 2 and for all subsequent cycles (i.e., after a precipitating event in a prior cycle of therapy) will be allowed per growth factor/neutropenia management guidelines and physician discretion. This GCSF use would potentially boost the neutrophil counts and thus prevent SN from occurring. The imbalance of GCSF use between the treatment group may potentially bias the between-treatment comparison of the occurrence of SN during Induction. Therefore, the hypothetical strategy (data after ICE will not be used) will be used for a sensitivity analysis.

Key Secondary Estimand

Overall Survival

To evaluate the effect of trilaciclib on OS compared with placebo.

Population:	The mITT population
Treatment:	Trilaciclib versus placebo administered prior to FOLFOXIRI/bevacizumab
Variable:	See Section 8.1.2
Summary measure:	HR from stratified Cox proportional hazard model with the fixed term of treatment and stratification factors at randomization

Handling of Intercurrent Events for Key Secondary Estimand

Overall Survival

Overall survival is considered the most reliable cancer endpoint when studies can be conducted to adequately assess survival. It is usually the preferred endpoint (FDA Guidance Dec. 2018, EMA/CHMP Guidance Sept. 2017). As mentioned in the FDA Guidance, the disadvantages of using OS as an endpoint include the following: (1) noncancer deaths are included; (2) may be affected by switch-over of control to treatment or subsequent therapies; (3) requires longer follow-up.

In this study, OS includes all deaths observed in the study regardless of cause (i.e., noncancer deaths as well as cancer-related deaths) for all randomized patients (the ITT population). The switch-over of control to treatment is not allowed in this study so it will not be considered as an ICE. Therefore, the following ICEs are identified for the primary estimand:

- Subsequent anticancer therapy
- Study discontinuation including lost to follow-up
- Curative intent surgical resection

The following strategies will be used for each of the above ICEs:

ICE	Primary	Sensitivity
1. Subsequent anticancer therapy	Treatment Policy Strategy	None
2. Study discontinuation including lost-to-follow up	Treatment Policy Strategy	None
3. Curative intent surgical resection	Treatment Policy Strategy	None

Justification for Primary and Sensitivity Strategies of ICE

1. Subsequent anticancer therapy

For the SAT, the treatment policy strategy is planned for the primary analysis of OS, in which all survival data collected over the course of the study are included regardless of the use of SAT. Treating SAT as a potential composite event for death would put two events with vastly different impacts on patients at the same level; therefore, there will be no sensitivity analysis for survival.

2. Study discontinuation

It is acknowledged that there are various reasons for patients to discontinue from the study which will potentially impact the estimate of treatment effect on OS in the situation that dropouts are not at random but associated with the treatment received in the study (i.e., the censoring is informative). However, there is no formal way to identify whether censorings are non-informative or informative. Therefore, the treatment policy strategy (i.e., the occurrence of the ICE was ignored) will be used as the primary analysis. Similarly, treating study discontinuation as a potential composite event for death would put two events with vastly different impacts on patients at the same level; therefore, there will be no sensitivity analysis for this ICE.

3. Curative intent surgical resection

For OS, this ICE will be treated similarly as SAT. Therefore, treatment policy strategy (i.e., the occurrence of the ICE was ignored) is planned for the primary analysis of OS, and there will be no sensitivity analysis for OS.

APPENDIX 3. CUSTOMIZED MedDRA QUERIES FOR TRILACICLIB AESIs

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