Protocol Title: A Phase 2, Randomized, Open-Label Study of Trilaciclib Administered with First-Line Platinum-Based Chemotherapy and Avelumab Maintenance Therapy in Patients with Untreated, Locally Advanced or Metastatic Urothelial Carcinoma (PRESERVE 3)

Protocol Number: G1T28-209

Compound: Trilaciclib for Injection, 300 mg/vial

Study Phase: 2

Study Name: PRESERVE 3

Sponsor Name: G1 Therapeutics, Inc.

Legal Registered Address: G1 Therapeutics, Inc.
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Regulatory Agency Identifier Numbers: IND: 156967
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Approval Date: 03 February 2022 (Version 3.0)

Previous Version (Amendment 1): 13 April 2021 (Version 2.0)

Original protocol: 22 February 2021 (Version 1.0)

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

I have read and understand the contents of this clinical protocol, Version 3.0, for Study G1T28-209 dated 03 Feb 2022 and I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of the study.

[redacted] PPD

[redacted] PPD

G1 Therapeutics, Inc.

[redacted]

Date

INVESTIGATOR'S AGREEMENT

Clinical Study Protocol G1T28-209: A Phase 2, Randomized, Open-Label Study of Trilaciclib Administered with First-Line Platinum-Based Chemotherapy and Avelumab Maintenance Therapy in Patients with Untreated, Locally Advanced or Metastatic Urothelial Carcinoma (PRESERVE 3)

Version 3.0 (Amendment 2) Issue Date: 03 February 2022

Replaces Version 2.0 (Amendment 1) Issue Date: 13 April 2021

Original Protocol (Version 1.0) Issue Date: 22 February 2021

I have read the G1T28-209 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Principal Investigator Signature	Date
Principal Investigator Name	Institution

1. SYNOPSIS

Name of Sponsor/Company: G1 Therapeutics, Inc.		
Name of Investigational Product: Trilaciclib for Injection, 300 mg/vial		
Name of Active Ingredient: trilaciclib dihydrochloride (hereafter referred to as trilaciclib) (G1T28)		
Protocol Number: G1T28-209	**Phase:** 2	**Regions:** North America, Europe
Title of Study: A Phase 2, Randomized, Open-Label Study of Trilaciclib Administered with First-Line Platinum-Based Chemotherapy and Avelumab Maintenance Therapy in Patients with Untreated, Locally Advanced or Metastatic Urothelial Carcinoma (PRESERVE 3)		
Study centers: Approximately 45 centers		
Studied period (years): Approximately 34 months Estimated date first patient randomized: Q2 2021 Estimated date last patient completed: Q1 2024		

Objectives:

Primary:

To evaluate the anti-tumor efficacy of trilaciclib when combined with platinum-based chemotherapy followed by trilaciclib administered with avelumab maintenance therapy as measured by progression-free survival (PFS) during the overall study.

Secondary:

To evaluate the anti-tumor efficacy of trilaciclib as measured by the objective response rate (ORR), disease control rate (DCR), duration of objective response (DOR), PFS in the maintenance period, overall survival (OS), and probability of survival at Month 16; evaluate the myeloprotective effects of trilaciclib on chemotherapy-induced myelosuppression; and assess the safety and tolerability of trilaciclib in patients receiving platinum-based chemotherapy followed by avelumab maintenance therapy.

Study Design:

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

Approximately 90 patients will be randomly assigned (1:1) to one of two treatment arms:

- Arm A – platinum-based chemotherapy followed by avelumab maintenance therapy
- Arm B – trilaciclib plus platinum-based chemotherapy followed by trilaciclib plus avelumab maintenance therapy

A Data Monitoring Committee (DMC) will monitor accumulating safety and anti-tumor response data with the first meeting planned when approximately 10 patients treated with trilaciclib + cisplatin or 10 patients treated with trilaciclib + carboplatin have completed at least 2 cycles of study treatment, whichever occurs first. The meetings will continue approximately every 6 months or as defined in the DMC charter while patients are on study treatment depending upon the enrollment rate. Additional

reviews may occur.

Standard of care platinum-based chemotherapy (with or without the addition of trilaciclib) will be administered intravenously (IV) in 21-day cycles and standard of care avelumab maintenance therapy (with or without the addition of trilaciclib) will be administered IV in 14-day cycles.

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

Study drugs will be administered as indicated in the respective dosage and administration sections of the synopsis.

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of randomization and completes at the End of Treatment Visit. Survival Follow-up assessments should occur every 3 months after the End of Treatment Visit (including assessments at Month 17 Day 1).

Patients enrolled in the study will be eligible to receive 4-6 cycles of platinum-based chemotherapy, and patients without progressive disease (PD) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines (i.e., with an ongoing complete response [CR], partial response [PR], or stable disease) after platinum-based chemotherapy will be eligible to receive avelumab maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first. Treatment visits will occur consecutively as planned, without interruption, except when necessary to manage toxicities or for administrative reasons (long weekends, holidays, weather conditions, etc.). There should be no more than 42 days between the start of each platinum-based chemotherapy cycle (with or without trilaciclib). Dosing delays >42 days between the start of each platinum-based chemotherapy cycle may be permitted on a case-by-case basis with the approval of the Investigator and Medical Monitor. There should be no more than 56 days between doses of avelumab maintenance therapy (with or without trilaciclib). Dosing delays >56 days between doses of avelumab may be permitted on a case-by-case basis with the approval of the Investigator and Medical Monitor. Avelumab maintenance therapy (with or without trilaciclib) should begin at a minimum of 4 and not more than 10 weeks after the last dose of platinum-based chemotherapy (with or without trilaciclib). Criteria which patients must meet in order to receive study drug on Day 1 and on Day 8 of each chemotherapy cycle are provided in the full protocol.

An End of Treatment Visit will occur approximately 14 days following a patient's last dose of study drug. Safety Follow-up Visits (which may be a phone call) will occur 30 days after the last dose of study drug and 90 days after the last dose of avelumab. Patients will be followed for survival approximately every 3 months (including an assessment at Month 17 Day 1) after the End of Treatment Visit. Survival Follow-up Visits may be done via telephone, email, or clinic visit. Unless otherwise decided by the Sponsor, the study will continue until at least 60% of patients enrolled in the study have died.

Methodology:

Sample Size Justification:

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

A total of 63 PFS events will be required to achieve 77% power to detect a hazard ratio (HR) of 0.6 in

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

Number of patients (planned):

Approximately 90 patients are planned in this study.

Diagnosis and main criteria for inclusion:

Patients ≥18 years of age at the time of signing the informed consent with locally advanced or metastatic urothelial carcinoma receiving first line treatment and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients must have documented, locally advanced (T4b, any N; or any T, N 2-3) or metastatic urothelial carcinoma (M1, Stage IV) (also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [UCC] of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra). Patients must have measurable disease as defined by RECIST v1.1, considered eligible to receive platinum-based chemotherapy and avelumab maintenance therapy, and no prior systemic therapy in the inoperable, locally advanced, or metastatic setting. A treatment-free interval > 12 months between the last perioperative/adjuvant treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting. Patients must have tumor tissue available from a metastatic or locally recurrent urothelial carcinoma lesion (archival or fresh biopsy). Patients must also have adequate organ function as demonstrated by the laboratory values.

Investigational product, dosage, and mode of administration:

Trilaciclib

In each chemotherapy cycle at Day 1 and Day 8, a dose of trilaciclib 240 mg/m^2 reconstituted and diluted in 250 mL of dextrose 5% in water (D5W) or normal saline (sodium chloride solution 0.9%) will be administered as a 30-minute IV infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered. If administration of platinum-based chemotherapy is skipped or discontinued, trilaciclib will also be skipped or discontinued.

In each avelumab maintenance cycle at Day 1, a dose of trilaciclib 240 mg/m^2 reconstituted as described above will be administered as a 30-minute IV infusion completed within 4 hours prior to the start of avelumab on each day avelumab is administered. If administration of avelumab maintenance therapy is delayed or skipped, then trilaciclib should be administered as scheduled. If administration of avelumab maintenance therapy is permanently discontinued, trilaciclib will also be permanently discontinued.

Duration of treatment:

Patients enrolled in the study will be eligible to receive 4-6 cycles of platinum-based chemotherapy followed by avelumab maintenance therapy (with or without trilaciclib) until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first. In specific circumstances, study treatment may continue beyond disease progression with approval from the Medical Monitor.

Reference therapy, dosage, and mode of administration:

Platinum-based chemotherapy

Gemcitabine 1000 mg/m^2 by IV infusion on Day 1 and Day 8 of each 21-day chemotherapy cycle.

Cisplatin eligible: cisplatin 70 mg/m^2 administered IV on Day 1 of each 21-day chemotherapy cycle.

Gemcitabine should be administered before cisplatin.

Cisplatin ineligible: carboplatin using Calvert formula with a target area under the curve (AUC) = 4.5 administered IV on Day 1 of each 21-day chemotherapy cycle. Gemcitabine should be administered before carboplatin.

Other platinum-based chemotherapies, such as methotrexate/carboplatin/vinblastine for example, are not permitted in this study.

Avelumab Maintenance Therapy

Avelumab 800 mg administered IV on Day 1 of each 14-day maintenance cycle as a 60-minute infusion. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory for the first 4 infusions. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity or prior infusion reactions.

Criteria for evaluation:

Efficacy:

Anti-tumor efficacy assessments include PFS, ORR (unconfirmed and confirmed), DCR, DOR, OS, and the probability of survival at Month 16. Tumor response criteria will be based on RECIST v1.1. Myelosuppression endpoints will be assessed based on hematology assessments, myelosuppression-related adverse event (AE) details, dose reductions/delays and supportive care interventions (including transfusions).

Safety:

Safety will be evaluated by monitoring AEs, clinical laboratory test results (hematology, clinical chemistry), vital sign measurements (blood pressure, heart rate, and oral body temperature), 12-lead safety electrocardiogram (ECG) results, dose modifications, and physical examination findings.

Pharmacokinetics:

The pharmacokinetics (PK) of trilaciclib and metabolites, cisplatin and avelumab will be determined using a non-linear mixed effects modeling approach.

Pharmacodynamics:

Pharmacodynamics may be assessed using peripheral blood and tumor biopsies to evaluate potential markers of response and resistance, including immune markers.

Statistical methods:

Unless otherwise specified, all analyses for the efficacy and safety endpoints will be conducted on data collected from both the chemotherapy period and the maintenance period in all patients irrespective of which platinum-based treatment (cisplatin and/or carboplatin) was administered as of the data cutoff date determined for a specific analysis.

Summary statistics will be provided by treatment group for all endpoints, when appropriate. Categorical variables will be summarized by counts and percentages, while continuous variables will be summarized by mean, standard deviations, median, 25% and 75% percentiles, and minimum and maximum values.

Patients will be randomized according to the stratification factors of presence of visceral metastasis (yes or no) and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin). When appropriate, presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin) will be included in statistical models for efficacy analyses with the strata information as entered in the Interactive Web Response System at the time of randomization.

Analysis population

The following analysis populations are defined for the study.

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

The response evaluable (RE) population includes all patients who are in the ITT population and who have measurable (target) tumor lesion(s) at baseline tumor assessment and either (i) have at least 1 post-baseline tumor assessment, or (ii) do not have post-dose tumor assessment but have clinical progression as noted by the Investigator, or (iii) died due to disease progression prior to their first post-baseline tumor scan. Analyses using this analysis population will be conducted according to the randomly assigned treatment. The RE population will be the primary analysis set for tumor response analyses.

The safety population includes all randomized patients who received at least 1 dose of any study drug. Analyses using the safety population will be conducted according to the actual treatment received. All safety analyses will be conducted using the safety population.

The PK population will include all patients who received at least one dose of trilaciclib or cisplatin or avelumab and have evaluable PK data.

Statistical analysis methods for primary and secondary endpoints

Analysis for primary efficacy endpoint

The primary efficacy endpoint, PFS (months) during the overall study, is defined as the time from the date of randomization to the date of documented radiologic disease progression per RECIST v1.1 or death due to any cause, whichever comes first regardless of in which treatment period the event occurs. For patients who do not experience PD or are alive at time of performing the PFS analysis, PFS will be calculated per censoring rules detailed in the statistical analysis plan (SAP). The primary analysis for PFS will be conducted at the time when 63 patients have radiographic-determined disease progression or died. The treatment effect on PFS will be primarily evaluated using a stratified log-rank test accounting for the two stratification factors. The magnitude of the treatment effect will be estimated by an HR (Arm B versus Arm A) using a stratified Cox proportional hazards model controlling for the two stratification factors. The 80% confidence interval (CI) will be generated for the HR. The Kaplan-Meier plots will be produced for PFS, respectively. Analysis of PFS will be based on the ITT population.

Analysis for secondary anti-tumor efficacy endpoints

ORR will be evaluated at the time when all randomized patients have finished chemotherapy and at the end of the treatment phase. ORR in the chemotherapy period is defined as the proportion of patients with best overall response (BOR) of confirmed or unconfirmed CR or PR. Unconfirmed CR or PR will be only allowed if there is lack of time to perform confirmed tumor scan in the chemotherapy period before the patient enters the maintenance period. ORR in the maintenance period is defined as the proportion of patients with BOR of confirmed CR or PR as determined using all tumor scan data from the maintenance period. ORR during the overall study is defined as the proportion of patients with BOR of confirmed CR or PR as determined using all tumor scan data from both chemotherapy and maintenance periods. 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 stratified Cochran–Mantel–Haenszel (CMH) method to account for the two stratification factors. The adjusted proportion difference (Arm B – Arm A) and its 95% CI will be calculated using CMH weight (as described in Kim, 2013). ORR will be analyzed based on the RE population. Other tumor response related endpoints will be defined similarly for different study periods.

In addition to PFS during the overall study, PFS in the maintenance period will be analyzed using similar statistical approaches. PFS in the maintenance period is defined as the time from the date of entering the maintenance period to the date of documented radiologic disease progression per RECIST v1.1 or death due to any cause in that period, whichever comes first. PFS in maintenance period will be analyzed based on the ITT population with at least a visit in the maintenance period.

OS (months) during the overall study is defined as the time from the date of randomization to the date of death for patients who died in the study due to any cause or the time to the last contact date known to be alive for those who survived as of the data cutoff date for the planned OS analysis (censored cases). In addition, OS in the maintenance period will also be analyzed. For OS in maintenance period, the date of entering the maintenance period will be used as the start time in the OS calculation. OS in maintenance phase will be analyzed based on the ITT population with at least one visit in the maintenance period. The treatment effect on OS will be evaluated by applying the same statistical models used for PFS analysis. Survival probability at Month 16 will be estimated using Kaplan-Meier method along with its two-sided 95% confidence interval (CI) (Kalbfleisch, 1980) for each treatment group, based on the ITT population.

Analysis for safety endpoints

Safety and tolerability will be assessed by AEs, dose modifications, laboratory tests, and vital signs. All safety data will be summarized using descriptive statistics by treatment group using the safety population. Adverse events are defined as those events occurring or worsening after treatment has begun on this study. Adverse event data will be coded to system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The severity (toxicity grades 1-5) of AEs will be graded by Investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Any AE, AEs related to each component of study treatment, AEs leading to study drug discontinuation, dose reductions, cycle delays, trilaciclib adverse events of special interest (AESIs), and avelumab AESIs will be summarized by system organ class, preferred term, and CTCAE grade, as appropriate. For laboratory assessments and vital signs, observed values and changes from baseline will be summarized by treatment group. For serum chemistry and hematology laboratory parameters, clinical labs will be characterized according to CTCAE toxicity grade from 1 to 5, Version 5.0 when possible, and the number and percentage of patients within each CTCAE grade will be summarized for the overall treatment period as well as for each cycle. Both scheduled and unscheduled data will be included in the safety evaluation.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aRR	adjusted relative risk
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCG	bacille Calmette-Guérin
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BOR	best overall response
BSA	body surface area
CBC	complete blood count
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CIM	chemotherapy-induced myelosuppression
CMH	Cochran–Mantel–Haenszel
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CYP	cytochrome P450
D5W	dextrose 5% in water

Abbreviation	Definition
DCR	disease control rate
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DOR	duration of response
DSN	duration of sever neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
E/P/A	etoposide/carboplatin/atezolizumab
ESA	erythropoiesis stimulating agent
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FDA	Food and Drug Administration
FDG	[^{18}F]-fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FN	febrile neutropenia
FSH	follicle stimulating hormone
G_1	gap 1 phase of the cell cycle
G1T28	trilaciclib; formerly G1T28-1
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GINA	Global Initiative for Asthma
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	hazard ratio
HRT	hormone replacement therapy
HSPC	hematopoietic stem and progenitor cell
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitors

Abbreviation	Definition
ICR	independent central review
IEC	independent ethics committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
INR	International Normalized Ratio
irAE	immune-related AE
IRB	institutional review board
irPD	immune-related disease progression
ITT	Intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
LFT	liver function test
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
M-CAVI	methotrexate/carboplatin/vinblastine
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRI	magnetic resonance imaging
MRP1 or 2	multidrug resistance protein 1 or 2
NaF	sodium fluoride
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OAT1 or 3	organic anion transporter 1 or 3
OATP1B1 or 1B3	organic anion transporting polypeptide 1B1 or 1B3
OCT1 or 2	organic cation transporter 1 or 2
ORR	objective response rate
OS	overall survival
PAM50	Prosigna Breast Cancer Prognostic Gene Signature Assay
PET	Positron Emission Tomography
PCS	potentially clinically significant

Abbreviation	Definition
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PTFE	polytetrafluorethylene
PVG	Pharmacovigilance
RB	retinoblastoma gene
RBC	red blood cell
RE	Response Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SN	severe neutropenia
SUSAR	suspected unexpected serious adverse reactions
TCC	transitional cell carcinoma
TCR	T cell receptor
TNBC	triple-negative breast cancer
TURBT	transurethral resection of bladder tumor
UCC	urothelial cell carcinoma
ULN	upper limit of normal
US	United States

4. INTRODUCTION

4.1. Urothelial Carcinoma

Bladder cancer is the most common malignancy involving the urinary system and is the sixth most common cancer in the United States (US) (NCCN, 2020). Approximately 2.4% of the US population will be diagnosed with bladder cancer at some point during their lifetime; the median age at diagnosis is 73 years and it is rarely diagnosed in people less than 40 years of age (NCCN, 2020; SEER, 2020). The rates of new cases and deaths were 20.0 and 4.3 per 100,000 men and women per year, respectively (using age-adjusted rates and based on 2013-2017 cases and 2014–2018 deaths) (SEER, 2020; NCCN, 2020).

Urothelial carcinoma, also known as transitional cell carcinoma (TCC), urothelial bladder cancer, or urothelial cell carcinoma (UCC) of the urinary tract, is the predominant histologic type in the US and Europe, where it accounts for 90% of all bladder cancers (NCCN, 2020). The overall 5-year survival rate for metastatic urothelial carcinoma is approximately 5.5%, which has remained unchanged over the past 25 years (SEER, 2020). Poor prognostic factors for survival in patients with metastatic urothelial carcinoma include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status <80%, and visceral metastasis (i.e., lung, liver, or bone; Bajorin, 1999). The presence of these unfavorable features was associated with a median survival of 4 months compared with 18 months in patients without these features (Loehrer, 1992). In addition, a Phase 3 study in second-line urothelial carcinoma comparing vinflunine with best supportive care identified presence of visceral involvement (i.e., liver or lung metastasis) one of the strongest prognostic factors associated with overall survival (OS) (Bellmunt, 2009).

In addition to the predictors of poor outcomes described above, chemotherapy-induced immunosuppression, a known side effect of platinum-based chemotherapy regimens, may also affect anti-tumor efficacy due to an inability of the host immune system to effectively mount a response against the cancer. Therefore, preserving the bone marrow from the cytotoxic effects of chemotherapy and potentially enhancing the immune system has the potential to maximize the anti-tumor activity of the chemotherapy while minimizing myelotoxicity.

While urothelial cancer has one of the highest mutation burdens among all types of cancer which is a known predictor of treatment response to immune checkpoint inhibitors (Crispen, 2020; Cancer Genome Atlas Network, 2014), the clinical efficacy of cancer immunotherapy is limited due to tumor-induced immune suppression and immune tolerance in urothelial carcinoma which is characterized by high levels of myeloid-derived suppressor cells (MDSCs), up-regulation of programmed death-ligand 1 (PD-L1) expression and tumor infiltration of immunosuppressive cells including regulatory T cells (Crispen, 2020). Therefore, coadministration of trilaciclib to re-activate the immune system and an immune checkpoint inhibitor (ICI) has the potential to further enhance the anti-tumor immune response and generate a greater anti-neoplastic effect than immunotherapy alone.

While the combination of ICIs with chemotherapy have indicated a meaningful step forward for the treatment of patients with PD-L1 positive advanced/metastatic urothelial carcinoma, it should be noted that due to the potential treatment toxicities associated with ICIs, not all patients with

PD-L1 positive urothelial carcinoma are appropriate candidates for ICI treatment and, as would be expected, the patient population with PD-L1 negative urothelial carcinoma derived only limited benefit. Overall, the urothelial carcinoma patient population continues to represent an area of high unmet medical need. Novel therapeutic options that can offer similar or better anti-tumor efficacy without the associated high-grade toxicities are clearly needed.

4.2. Treatment of Metastatic Urothelial Carcinoma

4.2.1. Platinum-Based Chemotherapy

Cisplatin-based chemotherapy became the standard first-line treatment for metastatic urothelial carcinoma in the 1980s, with long-term remissions observed in ~10% of patients (Galsky, 2020). While patients administered platinum-based chemotherapy have experienced clinical benefit (objective response in 40 to 50% of patients; disease control in 75 to 80%), most have disease progression within approximately 9 months, with the median OS 14 to 15 months for cisplatin-based-regimens and 9 to 10 months with carboplatin-based regimens (von der Maase, 2005; Galsky, 2012; Gartrell, 2017; Balar, 2017; Bamias, 2018). However, about 50% of patients with metastatic urothelial carcinoma are not eligible to receive cisplatin because of renal dysfunction or Eastern Cooperative Group (ECOG) performance status of 2, or both. Furthermore, hearing loss, Grade 2 neuropathy, heart failure, and age-associated diminished renal function may also confer cisplatin ineligibility (Dash, 2006; Galsky, 2011; Galsky, 2011). Carboplatin is often substituted for cisplatin in such patients, but it is associated with inferior outcomes (Galsky, 2011; Galsky, 2012). In addition, platinum-based chemotherapy regimens are associated with chemotherapy-induced myelosuppression. In the Phase 3 IMvigor130 study, 37% of patients in the gemcitabine/carboplatin arm experienced Grade 3 or 4 neutropenia, 21% experienced Grade 3 or 4 thrombocytopenia, and 40% experienced Grade 3 or 4 anemia. (Galsky, 2020). Thus, there remains a significant unmet medical need for well-tolerated therapies with improved anti-tumor and survival outcomes.

4.2.2. Immune Checkpoint Inhibitors

The first use of immunotherapy in patients with advanced urothelial carcinoma began in 1976 with the tuberculosis vaccine bacille Calmette-Guérin (BCG) and is used as locoregional therapy after surgical resection of non-muscle-invasive disease (Morales, 1976; Shelley, 2001). Multiple immunotherapies including interferon (IFN)-α, interleukin (IL)-2, IL-12, and IL-10 have been investigated, either as adjuncts with BCG or as a solo replacement therapy (Kamat, 2001; Askeland, 2012). Years later, Wang and colleagues analyzed the gene expression patterns of 32 different cancer types from The Cancer Genome Atlas and created a tumor immunogenicity score for each cancer type. Tumor immunogenicity determined by two factors (the antigenicity of tumor cells and the processing and presentation of tumor antigens) revealed that urothelial carcinoma had one of the higher tumor immunogenicity scores (Wang, 2019), indicating that it is a prime candidate for ICI treatment.

Expression of PD-L1 has been associated with poor prognosis in urothelial carcinoma, with Nakanishi and colleagues being one of the first groups to observe an association between expression of PD-L1 and outcomes in urothelial carcinoma. In their study, PD-L1 expression was significantly associated with a high frequency of disease recurrence and poor survival rate (Nakanishi, 2007). Subsequently, the programmed cell death protein 1 (PD-1)/PD-L1 pathway

has emerged as an important biological pathway in urothelial carcinoma. The PD-1/PD-L1 interaction inhibits T-lymphocyte activation, proliferation, survival, and effector functions during anti-cancer immune response. Several tumors, including urothelial carcinoma, present with high rates of somatic mutations (Kandoth, 2013; Lawrence, 2013; Cancer Genome Atlas Network, 2014), possibly enhancing the host immune system's ability to recognize tumor cells as foreign and stimulate a T cell response (Chen, 2013). However, tumors may elude the immune response through the expression of PD-L1 in the tumor microenvironment (Dong, 2002), making them potential targets of ICI therapies.

PD-1/PD-L1inhibitors are the most recent systemic therapies developed for metastatic urothelial carcinoma, both for first-line treatment of cisplatin-ineligible patients and for patients with disease progression despite platinum-based chemotherapy, as well as a maintenance treatment for patients who have not progressed on platinum-based chemotherapy (Massard, 2016; Rosenberg, 2016; Apolo, 2017; Balar, 2017; Balar, 2017; Sharma, 2017; Powles, 2018; Galsky, 2020; Powles, 2020). Indeed, ICIs have demonstrated significant and durable response in patients with advanced urothelial carcinoma. The US Food and Drug Administration (FDA) has approved the PD-L1 inhibitors avelumab, atezolizumab and durvalumab as well as the PD-1 inhibitors nivolumab and pembrolizumab for patients with urothelial carcinoma (NCCN, 2020). Avelumab, pembrolizumab, nivolumab, and durvalumab are approved for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels (Imfinzi®, 2017; Opdivo®, 2018; Bavencio®, 2020, Keytruda®, 2020). In March 2021, as part of an industry-wide assessment of indications based on accelerated approval, Roche in consultation with the FDA withdrew the indication for atezolizumab in patients with urothelial carcinoma following platinum-based chemotherapy. Additionally, atezolizumab and pembrolizumab are approved as a first-line treatment option for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-based chemotherapy regardless of PD-L1 expression (Keytruda, 2020; Tecentriq, 2020). Finally, avelumab is approved for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy (Bavencio, 2020 [US]; Bavencio, 2020 [EU]).

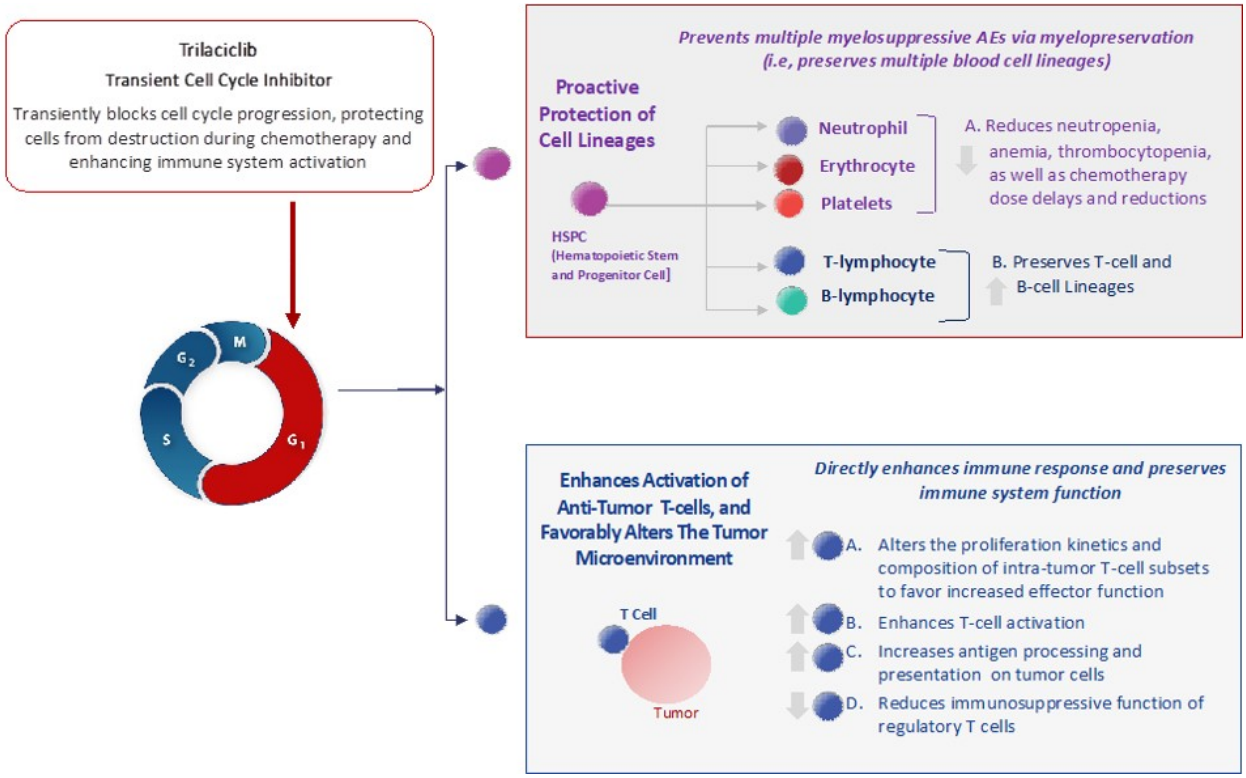
While the combination of ICIs with chemotherapy have indicated a meaningful step forward for the treatment of patients with PD-L1 positive advanced/metastatic urothelial carcinoma, it should be noted that due to the potential treatment toxicities associated with ICIs, not all patients with PD-L1 positive urothelial carcinoma are appropriate candidates for ICI treatment and, as would be expected, the patient population with PD-L1 negative urothelial carcinoma derived only limited benefit. In addition to the limitations described above, chemotherapy-induced immunosuppression, a known side effect of platinum-based chemotherapy regimens, may also affect anti-tumor efficacy due to an inability of the host immune system to effectively mount a response against the cancer. Therefore, preserving the bone marrow from the cytotoxic effects of chemotherapy, in addition to preserving and enhancing the immune system potentially through T cell receptor (TCR) modulation, has the potential to maximize the anti-tumor activity of the chemotherapy while minimizing myelotoxicity.

Novel therapeutic options that can offer similar or better anti-tumor efficacy without the associated high-grade toxicities are needed.

4.3. Urothelial Carcinoma and Trilaciclib

Trilaciclib is a highly potent and selective, reversible, cyclin-dependent kinase (CDK) 4/6 inhibitor that preserves hematopoietic stem and progenitor cells (HSPCs) as well as immune system function during chemotherapy (myeloprotection) in addition to directly enhancing anti-tumor immunity (anti-cancer efficacy) (Figure 1). Both HSPCs and lymphocyte proliferation are dependent on CDK4/6 activity (Kozar, 2004; Malumbres, 2004; Ramsey, 2007; Horsley, 2008) and become arrested in the gap 1 (G_1) phase of the cell cycle upon exposure to trilaciclib (He, 2017). This trilaciclib-induced transient cell cycle arrest has been demonstrated to provide resistance to chemotherapy-induced cell damage by preventing HSPCs from proliferating in the presence of cytotoxic chemotherapy and favorably altering the tumor immune microenvironment through transient T cell inhibition when combined with chemotherapy (He, 2017; Bisi, 2016; Lai, 2020). In February 2021, the United States Food and Drug Administration (FDA) approved trilaciclib (COSELA™) as a treatment to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

Figure 1: Trilaciclib Transiently Arrests Normal Cells to Prevent Chemotherapy-Induced Myelosuppression and Improve Anti-Tumor Efficacy



As stated previously, patients treated with platinum-based chemotherapy experience chemotherapy-induced myelosuppression. Whereas current treatments for chemotherapy-induced myelosuppression are lineage specific, used after the damage to HSPCs has occurred, and place patients at risk for additional toxicities, trilaciclib improves the overall chemotherapy experience for patients by the prevention of damage to HSPCs and therefore chemotherapy-induced myelosuppression, thus resulting in an overall improved safety profile and reduced utilization of available standard of care treatments.

Three randomized, double-blind, Phase 2 clinical trials evaluating trilaciclib/placebo administered prior to chemotherapy in patients with small cell lung cancer (SCLC) have demonstrated in a variety of clinical settings (patients receiving first-, second-, or third-line SCLC treatments with several different classes of chemotherapy) that trilaciclib can prevent chemotherapy-induced myelosuppression as measured by multiple endpoints (Weiss, 2019; Hart, 2019; Daniel, 2019). In an analysis of integrated data from all three studies, the delivery of trilaciclib prior to chemotherapy results in a 4-day reduction in the duration of severe neutropenia (DSN) in Cycle 1 and an approximately 76% reduction (52.9% placebo to 11.4% trilaciclib) in the occurrence of severe neutropenia (SN) during chemotherapy treatment. The occurrence of red blood cell (RBC) transfusions on or after 5 weeks on study was reduced by almost half from 26.1% in those treated with placebo to 14.6% in those receiving trilaciclib with an associated 31.9% to 20.3% reduction in the rates of Grade 3 or 4 anemia. Grade 3 or 4 thrombocytopenia was decreased from 36.1% to 19.5% with the addition of trilaciclib, and diarrhea was decreased from 17.8% to 13.1%.

The exploratory patient-reported outcome endpoints in these patients suggested that trilaciclib administered prior to chemotherapy may offer potential benefit in multiple aspects of health-related quality of life with a greater magnitude of effect observed for fatigue and anemia symptoms and functional limitations (Weiss, 2019). An analysis of integrated fatigue subscale data from Functional Assessment of Cancer Therapy – Anemia (FACT-An) in the three studies showed that trilaciclib delayed the median time to deterioration by approximately 5 months for fatigue (7.03 months in the trilaciclib group vs. 2.33 months in the placebo group, hazard ratio [HR]: 0.56 [0.37, 0.85]). In addition, these myeloprotection benefits were observed in the setting of minor improvements in progression-free survival (PFS) and OS as evidenced by hazard ratios (HRs) <1.0 in almost all clinical settings for trilaciclib compared to placebo. For more detailed information, refer to the trilaciclib Investigator's Brochure (IB).

In a randomized Phase 2 study (G1T28-04) in patients with triple-negative breast cancer (TNBC), the addition of trilaciclib to chemotherapy had a substantial impact on anti-tumor efficacy as measured by OS (as discussed below) but did not result in the striking statistically significant effects on chemotherapy-induced myelosuppression observed in the SCLC trials described previously. The differences between the observed results in the SCLC trials and those in the TNBC trial are hypothesized to result from differences in the key variables between the two clinical situations.

Unlike chemotherapy-induced myelosuppression, the effects of trilaciclib on anti-tumor efficacy are predicted to be primarily driven by the tumor type, chemotherapy type, and host, i.e., (1) the tumor type must be sufficiently responsive to chemotherapy such that maintenance of chemotherapy dose intensity is beneficial, (2) the tumor must be sufficiently immunogenic and

sensitive to the host cytolytic efforts as to see improvement in anti-tumor endpoints like OS, (3) the chemotherapy should promote immune activation, (4) the host must be able to tolerate the standard of care chemotherapy dose intensity, and (5) the host must be able to mount an effective cytolytic response against the tumor. In the SCLC trials, the addition of trilaciclib to the standard of care therapies provided modest improvement, to neutral effects, on measures of anti-tumor efficacy including objective response rate (ORR), PFS, and OS. These results are not surprising considering that SCLC is one of the most aggressive solid tumors, relapses quickly after completion of chemotherapy, has been shown to be relatively insensitive to multiple attempts to intensify the chemotherapy regimen beyond the current standard of care, and is not particularly immunogenic or sensitive to immune modulation. In contrast, TNBC has been shown to be immunogenic and more sensitive to immune modulation compared to SCLC (Semenova, 2015; He, 2017, Carvajal-Hausdorf, 2019; Liu, 2018). The observation that trilaciclib, when added to standard of care therapy in TNBC patients, improved anti-tumor efficacy outcomes provides support for the hypothesis that given urothelial carcinoma has been shown to be immunogenic (Wang, 2019) and responds to ICIs (Galsky, 2020; Powles, 2020), trilaciclib may enhance anti-tumor outcomes when added to platinum-based chemotherapy and avelumab maintenance therapy.

As discussed above, based on trilaciclib's mechanism of action (MOA), it was hypothesized that trilaciclib administered before chemotherapy could protect the bone marrow from the cytotoxic effects of chemotherapy, while also enhancing immune activity in patients with TNBC, thus potentially improving both safety and anti-tumor activity. Therefore, trilaciclib was evaluated in Study G1T28-04, a global, multicenter, randomized, open-label, Phase 2 clinical trial to evaluate the safety, efficacy, and pharmacokinetics (PK) of trilaciclib administered prior to gemcitabine/carboplatin chemotherapy for patients with locally recurrent/metastatic TNBC who had previously been treated with 0 to 2 lines of therapy in the metastatic setting. Patients were randomized 1:1:1 to one of two different trilaciclib + gemcitabine/carboplatin treatment regimens or gemcitabine/carboplatin alone.

In the Phase 2 G1T28-04 TNBC study, the addition of trilaciclib to chemotherapy resulted in improvements in anti-tumor efficacy as measured by OS (median OS duration in the control group was 12.6 months vs. not evaluable or 17.8 months in the two trilaciclib groups, HR: 0.31 [p=0.0016] and HR: 0.40 [p=0.0004], respectively) and by PFS (median PFS in the control group was 5.7 months vs. 9.4 months or 7.3 months in the two trilaciclib groups HR: 0.62 and 0.63, respectively; not statistically significant), and ORR (29.2% in the control group vs. 50.0% and 38.7% in the two trilaciclib groups, respectively; not statistically significant) (Tan, 2019; O'Shaughnessy, 2020).

The clinically meaningful anti-tumor efficacy results observed in Study G1T28-04 (a secondary endpoint) were noted across both of the trilaciclib treatment groups and in patients with both PD-L1 positive and negative tumors, and these benefits were observed for multiple anti-tumor efficacy endpoints, with ORR, PFS, and OS endpoints all showing numerical improvement with the addition of trilaciclib to chemotherapy compared with chemotherapy alone.

In addition, while the sample size in Study G1T28-04 was small, the results were generally consistent across patient subgroups, including CDK4/6 status. Patient tumors were characterized as CDK4/6 independent, dependent, or indeterminate using two established signatures (Prosigna Breast Cancer Prognostic Gene Signature Assay [PAM50] and Lehmann triple-negative breast

cancer type) (Prat, 2014; Lehmann, 2016; Asghar, 2017). As expected, these data suggest trilaciclib does not antagonize chemotherapy efficacy regardless of CDK4/6 status, including tumors that are CDK4/6 indeterminate or dependent (Tan, 2019; O'Shaughnessy, 2020). While some tumors have been shown to be predominantly CDK4/6 dependent, CDK2NA is lost in 20-30% of bladder cancers (Cancer Genome Atlas Network, 2014; Robertson, 2017), and preclinical studies have demonstrated some efficacy of CDK4/6 inhibition in bladder cancer (Choi, 2014; Damrauer, 2014). In addition, a Phase 2 trial evaluating palbociclib monotherapy in patients with metastatic urothelial carcinoma after failure of first-line platinum-based chemotherapy showed that palbociclib did not demonstrate meaningful activity as measured by PFS at 4 months, with RB status not correlating with response (Rose, 2018), suggesting bladder cancer is not as CDK4/6 dependent as expected. This information, along with the clinical data in TNBC, suggest trilaciclib will not antagonize the anti-tumor effects of chemotherapy in bladder cancer.

Lastly, to evaluate the effect of trilaciclib on T cell activation, peripheral blood was collected and the TCR was evaluated. Simpson clonality decreased over time in patients that received trilaciclib in addition to gemcitabine/carboplatin when compared to gemcitabine/carboplatin alone. Furthermore, after stratification above or below median Simpson clonality at baseline, an exploratory analysis showed patients above the median demonstrated a greater OS benefit with the addition of trilaciclib. In addition to a decrease in Simpson clonality, responders receiving trilaciclib prior to gemcitabine/carboplatin had more newly detected expanded clones compared with responders receiving gemcitabine/carboplatin alone. These data suggest trilaciclib enhances anti-tumor immunity through T cell activation leading to an anti-tumor response in TNBC (O'Shaughnessy, 2020).

4.4. Study Rationale

Trilaciclib is an intravenous (IV), short-acting, selective, and reversible CDK4/6 inhibitor that transiently arrests cells in the G_1 phase of the cell cycle. Trilaciclib was originally developed to preserve bone marrow function from chemotherapy (myeloprotection). An integrated analysis across three SCLC studies demonstrated this myeloprotection activity by reducing the rate and duration of severe neutropenia, reducing the rate of thrombocytopenia and anemia, and reducing the rate of RBC transfusions. Study G1T28-04, a Phase 2 study in metastatic TNBC patients showed a clinically meaningful OS benefit (a secondary endpoint) in patients receiving trilaciclib prior to chemotherapy versus chemotherapy alone; this benefit was observed across both trilaciclib treatment arms. Subgroup analyses demonstrated both PD-L1 positive and negative patients benefitted from the addition of trilaciclib. In addition to the improved OS results, Study G1T28-04 indicated an improvement in patient-reported outcomes as measured by the FACT scales, and a manageable safety profile.

Given the encouraging results of improved anti-tumor efficacy, myeloprotection, and patient outcomes observed in trilaciclib studies to date (Section 4.5.2), this exploratory Phase 2 clinical trial in patients with urothelial carcinoma receiving first-line treatment for advanced/metastatic disease is designed to assess whether or not trilaciclib can improve anti-tumor efficacy when administered prior to platinum-based chemotherapy followed by avelumab maintenance therapy and reduce the chemotherapy-induced myelosuppression observed with platinum-based chemotherapy.

4.5. Background

In February 2021, the United States Food and Drug Administration (FDA) approved trilaciclib (COSELA™) as a treatment to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

4.5.1. Summary of Nonclinical Data

A brief summary of the trilaciclib nonclinical data is provided in the following sections. Detailed information is presented in the trilaciclib IB.

Nonclinical data related to avelumab and gemcitabine/carboplatin/cisplatin are provided in the local prescribing information.

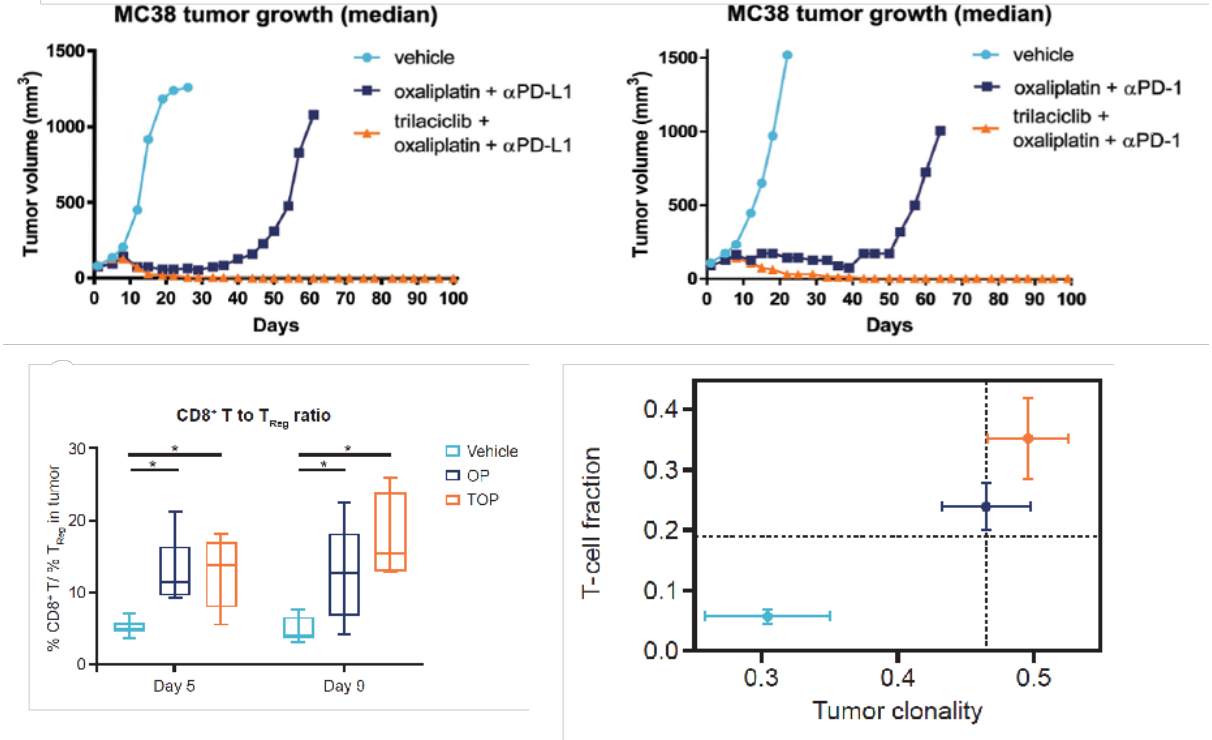
4.5.1.1. Pharmacology Studies

Through a structure-based design approach to optimize potency, selectivity, and drug metabolism and PK properties, G1 Therapeutics, Inc. identified trilaciclib as a highly potent inhibitor of CDK4 and CDK6 (half maximal inhibitory concentration values of 1 nM and 4 nM, respectively) that is highly selective for CDK4/Cyclin D1 versus CDK2/Cyclin E (>2500-fold selectivity). Trilaciclib also demonstrated reversible inhibition of CDK4/Cyclin D1, with an inhibition constant value of 0.78 nM.

The trilaciclib-induced G_1 arrest of HSPCs has been shown to be transient and readily reversible in both *in vitro* and *in vivo* models. *In vivo* analysis has demonstrated that trilaciclib administered prior to myelosuppressive chemotherapy leads to improved complete blood count (CBC) recovery of all blood lineages and increased survival. Specifically, in a model using the highly myelosuppressive chemotherapy 5-fluorouracil (5-FU), while the extent and duration of nadir in CBCs worsened after each cycle of 5-FU administered alone, trilaciclib administered prior to 5-FU ameliorated this worsening effect and the animals that received trilaciclib + 5-FU demonstrated a faster rate of recovery of CBCs compared with the 5-FU alone group following Cycle 4 (He, 2017).

Preclinical data have shown trilaciclib enhances immune activation and promotes anti-tumor immunity by differentially arresting cytotoxic and regulatory T cell subsets followed by a faster recovery of cytotoxic T lymphocytes than regulatory T cells in tumors. Specifically, the addition of trilaciclib to various chemotherapy/ICI treatment combinations resulted in enhanced tumor growth delay and durability of the antitumor response. Trilaciclib favorably modulated the proliferation of T cell subsets in the tumor microenvironment, consistent with an enhanced cytotoxic T cell response (Figure 2; Lai, 2020). This differential alteration of cell cycle kinetics between cytotoxic T lymphocytes and regulatory T cells results in a higher proportion of cytotoxic T lymphocytes than regulatory T cells, enhancement of T cell activation, and a decrease in regulatory T cell-mediated immunosuppressive functions (Chaikovsky and Sage, 2018; Deng, 2018; Goel, 2017; Schaer, 2018). Together, these events promote the cytotoxic T lymphocyte-mediated clearance of tumor cells. Therefore, these data support the hypothesis that trilaciclib-mediated transient proliferative arrest of T cells (protecting them from chemotherapy-induced damage), followed by activation of cytotoxic T lymphocytes in the context of fewer regulatory T cells led to the anti-tumor response observed.

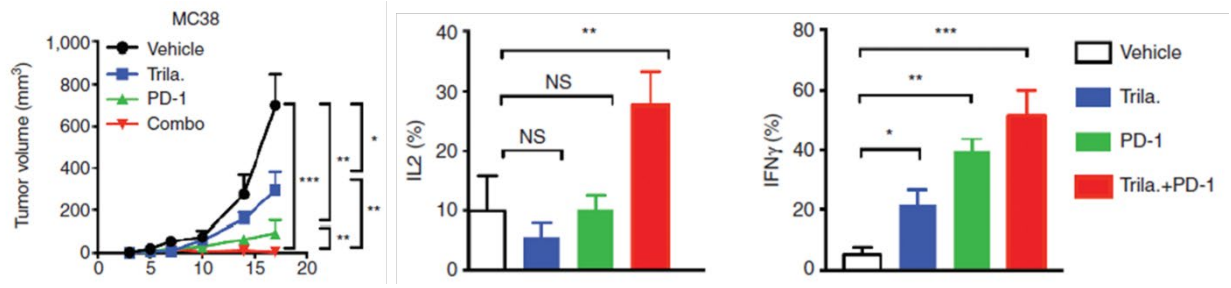
Figure 2: The Addition of Trilaciclib to Chemotherapy/Checkpoint Inhibitor Treatment Enhances Efficacy Through T Cell Activation



CD=cluster of differentiation; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; Treg=regulatory T cell.

Ex vivo and *in vivo* studies revealed that the inhibition of CDK4/6 by trilaciclib resulted in increased antitumor activity, particularly in conjunction with PD-1 blockade, and this effect was largely dependent on T cells (Deng, 2018). *In vivo* PD-1 blockade induced partial tumor growth inhibition in the murine colon carcinoma MC38 model and the addition of intermittent exposure to trilaciclib nearly eliminated tumor growth (Figure 3, LEFT). Profiling of tumor infiltrating lympocytes from MC38 tumors revealed that anti-PD-1 alone increased CD8+ IFNγ production but not CD4+ IL2 production (Figure 3, RIGHT and MIDDLE). Thus, in this model, PD-1 blockade increased the cytotoxicity of CD8+ T cells but did not increase T-cell proliferation through IL2. Addition of trilaciclib to PD-1 blockade resulted in an approximately 10-fold increase in the levels of IFNγ in CD8+ TILs and approximately 2-fold increase in CD4+ IL2 production. These data demonstrate that trilaciclib augmented anti-tumor immunity, which translated to an improved antitumor response that was largely dependent on the activity of T cells, thereby sensitizing tumors to immune checkpoint blockade.

Figure 3: Trilaciclib Augments Anti-PD-1 Antibody-Induced Antitumor Activity



Combination treatment of trilaciclib synergize anti–PD-1 antibody–induced antitumor immunity through T cells. (LEFT) Tumor growth curves of MC38 cells treated with trilaciclib or PD-1 antibody alone or in combination. MC38 murine cancer cells were injected subcutaneously into C57BL/6 mice. The mice were treated with trilaciclib 100 mg/kg intermittently (3 days on, 4 days off) with or without PD-1 antibody (200 μg/mouse, 3 times a week) as indicated starting from day 3 (MC38). Tumor volumes were monitored every 2–3 days. The graph shows representative results from two independent experiments (n = 8; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$). (MIDDLE and RIGHT) Quantification of cytokine production produced by MC38 tumor-infiltrating T lymphocytes. At the end of the treatment (day 17), mice were sacrificed and tumor infiltrating lymphocytes were isolated from the tumor for cytokine analysis for IL2 from CD4+ T cells (MIDDLE) and IFNγ from CD8+ T cells (RIGHT) (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).

Preclinical data have shown that in a highly CDK4/6 dependent estrogen receptor positive breast cancer model, intermittent trilaciclib dosing during the time of chemotherapy treatment did not negatively affect chemotherapy treatment. The lack of antagonism when trilaciclib was added to chemotherapy treatment was observed in multiple CDK4/6 dependent models (Sorrentino, 2018). While trilaciclib is not expected to directly impact tumor proliferation, it has the potential to greatly improve the current standard of care in urothelial carcinoma by protecting the bone marrow and immune system function during chemotherapy in addition to activating T cell mediated immunity and potentially enhancing anti-tumor activity.

4.5.1.2. Pharmacokinetic Studies

Pharmacokinetic studies in rats and dogs showed that the relationship between dose level and plasma exposure to trilaciclib was generally similar between males and females and did not change with repeated daily dosing. Exposure to trilaciclib increased with dose level, but not always proportionally.

In vitro analyses of direct and time-dependent inhibition suggest that drug interactions based on inhibition of cytochrome P450 (CYP)1A2-, 2B6-, 2C8-, 2C9-, 2C19-, and 2D6-mediated metabolic pathways are unlikely at clinical doses, however, the studies do suggest that drug interactions based on trilaciclib-mediated inhibition of CYP3A4-mediated metabolic pathways are possible, but clinical studies have confirmed no clinically significant drug-drug interaction (DDI) based on CYP3A (see Section 4.5.2.2 for additional details). Additionally, *in vitro* induction studies of the 3 major inducible CYP enzymes (CYP1A2, CYP3A4, and CYP2B6) in human hepatocytes suggest that trilaciclib-mediated induction is unlikely.

In vitro inhibition studies with membrane transporter model systems also suggest trilaciclib is unlikely to cause a DDI based on inhibition of breast cancer resistance protein-, bile salt export pump-, organic anion transporter 1 (OAT1)-, organic anion transporter 3 (OAT3)-, organic anion transporting polypeptide 1B1 (OATP1B1)-, p-glycoprotein-, multidrug resistance protein 1

(MRP1)-, multidrug resistance protein 2 (MRP2)-, or organic anion transporting polypeptide 1B3 (OATP1B3)-mediated transport.

However, *in vitro*, trilaciclib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1), multidrug and toxin extrusion 2-K (MATE2-K), organic cation transporter 1 (OCT1), and organic cation transporter 2 (OCT2) (see Section 4.5.2.2 for additional details).

4.5.2. Summary of Clinical Data

A brief summary of the trilaciclib clinical data is provided in the following sections. Detailed information is presented in the trilaciclib IB.

4.5.2.1. Efficacy

The safety and efficacy of administering trilaciclib prior to chemotherapy was tested in one completed and one ongoing Phase 1b/2 study (G1T28-02 and G1T28-03) and one ongoing and one completed Phase 2 study (G1T28-05 and G1T28-04) in patients with SCLC or TNBC. The Phase 2 portions of Studies G1T28-02, G1T28-03, and Study G1T28-05 were randomized, double-blind and placebo-controlled. Study G1T28-04 was randomized and included a control arm but was not double-blinded.

- Study G1T28-02 examined once-daily IV administration of either trilaciclib or placebo on Days 1 to 3 of each 21-day etoposide plus carboplatin (E/P) chemotherapy cycle in patients with treatment naïve extensive-stage SCLC.
- Study G1T28-03 examined once-daily IV administration of trilaciclib or placebo on Days 1 to 5 of each 21-day topotecan chemotherapy cycle in patients with previously treated extensive-stage SCLC.
- Study G1T28-05 examined once-daily IV administration of trilaciclib or placebo on Days 1 to 3 for a maximum of four 21-day cycles of E/P and atezolizumab, followed by monotherapy atezolizumab, in patients with treatment naïve extensive-stage SCLC.
- Study G1T28-04 examined once-daily IV administration of trilaciclib prior to gemcitabine and carboplatin in patients with metastatic TNBC who had received 0 to 2 lines of previous therapy in the metastatic setting. Patients received: 1) gemcitabine/carboplatin therapy only on Days 1 and 8 of a 21-day cycle, 2) trilaciclib and gemcitabine/carboplatin once daily on Days 1 and 8 of each 21-day cycle, OR 3) trilaciclib on Days 1, 2, 8 and 9 with gemcitabine/carboplatin on Days 2 and 9 of each 21-day cycle (further noted as Group 1, 2, or 3, respectively).

At the recommended phase 2 dose (RP2D) of 240 mg/m^2, across all three SCLC studies, trilaciclib administered prior to chemotherapy statistically significantly reduced the DSN in Cycle 1 and occurrence of SN (primary endpoints) compared with placebo. An integrated data analysis of the three SCLC studies (G1T28-02, G1T28-03, and G1T28-05) for 8 of the most relevant myelosuppression endpoints (neutrophils, RBCs, and platelets) demonstrated statistically significant, and clinically meaningful, improvements for trilaciclib over available therapies in 6 of 8 endpoints across multiple lineages. Importantly, these myeloprotection benefits come with an overall improved safety profile compared with available therapy, as

evidenced by reduced high grade treatment-emergent adverse events (AEs) across all SCLC studies, and no detriment to anti-tumor efficacy results. For a more detailed description of the results, refer to the trilaciclib IB.

Results from the TNBC Study G1T28-04 demonstrated that although the addition of trilaciclib at the RP2D to gemcitabine/carboplatin did not statistically significantly improve chemotherapy-induced myelosuppression as measured by the neutrophil-based endpoints of DSN in Cycle 1 and occurrence of SN, there were trends toward improvement in RBC and platelet-based measures. In addition, anti-tumor efficacy results demonstrated a clinically meaningful improvement in PFS and OS (Figure 4; Table 2). This meaningful anti-tumor efficacy was observed across multiple subgroups, including both PD-L1 positive and negative tumor types (Table 3), and in both trilaciclib groups compared with the control group.

Table 2: G1T28-04: Summary of Overall Survival and Progression-Free Survival (ITT Analysis Set)

Category	Group 1 Gem/Carbo (Day 1+8) (N=34)	Group 2 Gem/Carbo + Trilaciclib (Day 1+8) (N=33)	Group 3 Gem/Carbo + Trilaciclib (Day 1/2+8/9) (N=35)	Groups 2+3 (N=68)
Overall survival (months) (95% CI)[a, b]				
25%	5.8 (2.8, 9.7)	9.4 (3.4, 19.6)	8.8 (6.0, 15.3)	8.8 (6.0, 14.0)
Median	12.6 (6.3, 15.6)	NR (10.2, NR)	17.8 (12.9, 32.7)	19.8 (14.0, NR)
75%	17.8 (12.8, 25.0)	NR (NR, NR)	32.7 (19.8, NR)	NR (32.7, NR)
Comparison (treatment group versus Group 1)				
Adjusted HR (SE)[c]	NA	0.31 (0.111)	0.40 (0.125)	0.37 (0.101)
95% CI[c]	NA	0.15, 0.63	0.22, 0.74	0.21, 0.63
2-sided p-value[d]	NA	0.0016	0.0004	<0.0001
Progression-free survival (months) (95% CI)[a, b]				
25%	2.2 (1.2, 5.4)	5.3 (1.2, 7.9)	6.2 (1.2, 7.1)	5.9 (2.1, 6.5)
Median	5.7 (3.3, 9.9)	9.4 (6.1, 11.9)	7.3 (6.2, 13.9)	9.0 (6.4, 11.3)
75%	9.9 (8.3, 18.8)	13.0 (9.7, 24.1)	13.9 (9.0, NR)	13.9 (10.9, 15.6)
Comparison (Treatment Group versus Group 1)				
Adjusted HR (SE)[c]	NA	0.62 (0.209)	0.63 (0.212)	0.62 (0.180)
95% CI[c]	NA	0.32, 1.20	0.32, 1.22	0.36, 1.10
2-sided p-value[d]	NA	0.2099	0.1816	0.1291

CI=confidence interval; Gem/Carbo=gemcitabine/carboplatin; HR=hazard ratio; ITT=intent-to-treat; N=total number of patients in each treatment group; NA=not applicable; NR=not reached; OS=overall survival; SE=standard error.

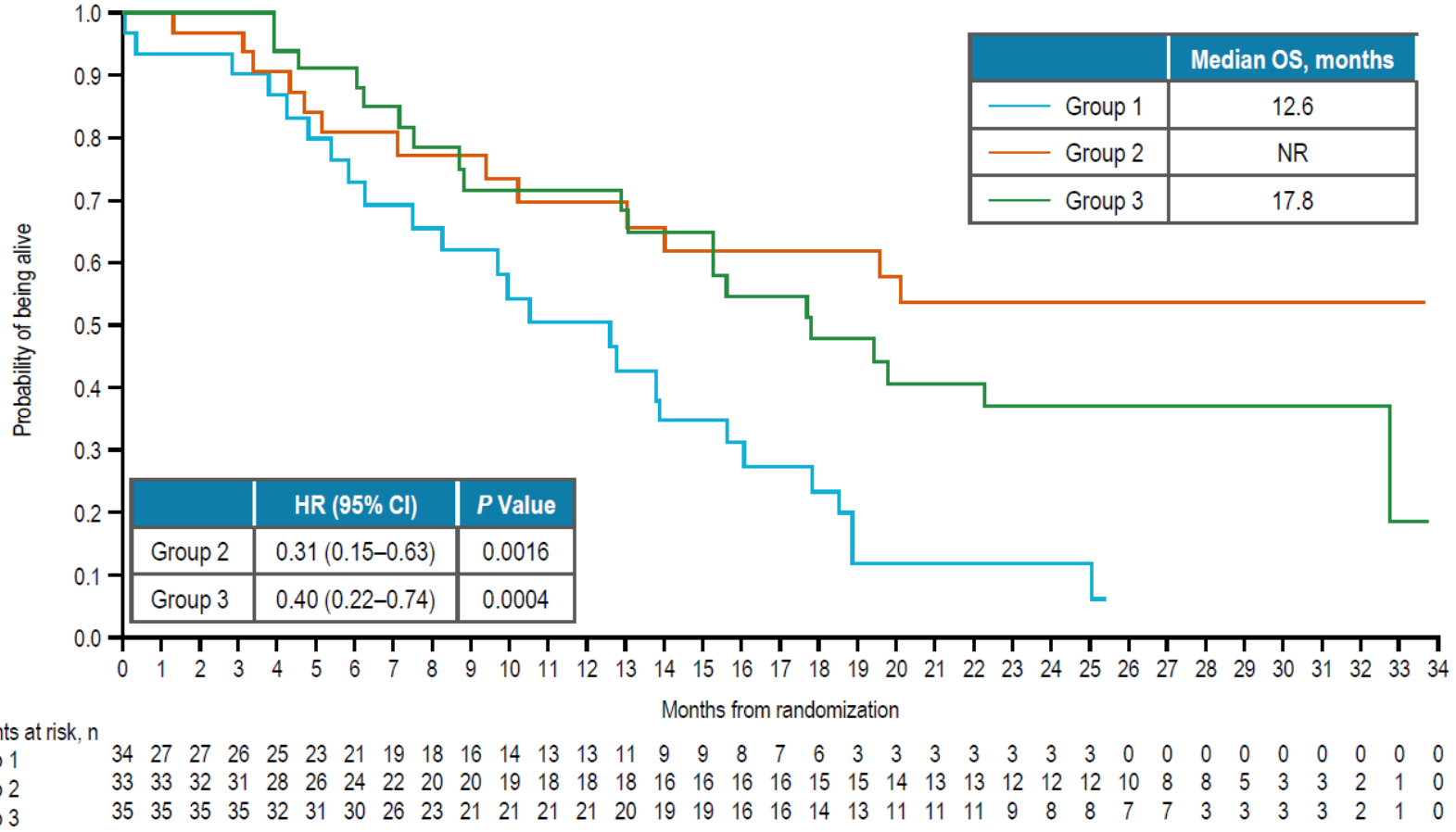
[a] Calculated using the Kaplan-Meier method

[b] OS reported from final database; PFS reported from earlier data cutoff on 15 May 2020.

[c] The HR and its 95% CI were calculated using the Cox regression model controlling for the stratification factors, namely, number of prior lines of therapy (0 versus 1 or 2) and liver involvement.

[d] P-value was calculated using the stratified log-rank test controlling for the two stratification factors.

Figure 4: G1T28-04: Overall Survival – Kaplan-Meier Curve (ITT Analysis Set)



CI=confidence interval; GC=gemcitabine and carboplatin; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; OS=overall survival.
Group 1: GC administered on Days 1 and 8 of 21-day cycles; Group 2: Trilaciclib and GC administered on Days 1 and 8 of 21-day cycles; Group 3: Trilaciclib administered on Days 1, 2, 8, and 9 and GC administered on Days 1 and 8 of 21-day cycles.
Note: The HR and its 95% CI comparing Group 1 and 2 and Group 1 and 3 were calculated using the Cox regression model with treatment and stratification factors of number of prior lines of therapy (0 versus 1 or 2) and liver involvement.
Note: P-values comparing Group 1 and 2 and Group 1 and 3 were calculated using the stratified log-rank test to account for the number of prior lines of therapy (0 versus 1 or 2) and liver involvement as the stratification factors.
Note: data generated from final database.

Table 3: G1T28-04: Tumor Response According to PD-L1 Status

	PD-L1 Positive				PD-L1 Negative			
	Group 1	**Group 2**	**Group 3**	**Group 2+ 3**	**Group 1**	**Group 2**	**Group 3**	**Group 2+ 3**
Patients analyzed	17	16	16	32	10	10	16	26
Median PFS, months (95% CI)[a]	5.4 (3.3-NR)	7.9 (6.1-NR)	10.9 (6.2-NR)	9.7 (6.2-15.5)	9.2 (8.3-NR)	11.9 (8.8-NR)	9.0 (6.4-NR)	9.4 (6.5-14.6)
HR (95% CI)	-	0.74 (0.3-1.7)	0.41 (0.2-1.1)	0.57 (0.3-1.2)	-	0.60 (0.2-1.9)	1.47 (0.5-4.3)	0.97 (0.4-2.5)
Median OS, months (95% CI)[a]	10.5 (6.3-18.8)	20.1 (10.2-NR)	32.7 (15.3-NR)	32.7 (17.7-NR)	13.9 (12.6-NR)	NR (9.4-NR)	17.8 (12.9-NR)	17.8 (13.1-NR)
HR (95% CI)	-	0.38 (0.2-1.0)	0.30 (0.1-0.8)	0.34 (0.2-0.7)	-	0.35 (0.1-1.2)	0.55 (0.2-1.4)	0.48 (0.2-1.2)

CI=confidence interval; HR=hazard ratio; NR=not reached; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.
Group 1: chemotherapy on Days 1 and 8; Group 2: trilaciclib and chemotherapy on Days 1 and 8; Group 3: trilaciclib along on Days 1 and 8 with chemotherapy on Days 2 and 9. HR values are comparisons between Group 2 and Group 1, Group 3 and Group 1, and between combined Groups 2 and 3 and Group 1.
[a] OS reported from final database; PFS reported from earlier data cutoff on 15 May 2020.

As mentioned in Section 4.5.1.1, there is a hypothetical risk that administration of trilaciclib prior to chemotherapy could decrease chemotherapy efficacy. This hypothetical risk is countered by the results observed in Study G1T28-04 which suggested that the addition of trilaciclib improves the anti-tumor efficacy of gemcitabine/carboplatin regardless of the CDK4/6 status of the TNBC tumor. Although TNBC tumors are predominantly classified as CDK4/6 independent (i.e., their replication is not sensitive to CDK4/6 inhibition), there is a small subset of patients whose tumors are classified as either CDK4/6 indeterminate or CDK4/6 dependent. When the TNBC population enrolled in Study G1T28-04 is divided into these subsets, evaluation of the anti-tumor efficacy in patients whose tumors are classified as CDK4/6 indeterminate or CDK4/6 dependent suggests that trilaciclib does not antagonize the anti-tumor effects of gemcitabine/carboplatin. Specifically, PFS and OS did not decrease when trilaciclib was added to gemcitabine/carboplatin in the most CDK4/6-dependent population (see trilaciclib IB).

4.5.2.2. Pharmacokinetics

Trilaciclib has a terminal half-life of approximately 14 hours and undergoes extensive metabolism. Mild hepatic impairment and mild and moderate renal impairment had no effect on trilaciclib exposure. Population PK analysis indicated that age, gender, weight and race had no clinically relevant effect on the systemic exposure of trilaciclib. For more information about PK profile of trilaciclib, please refer to the trilaciclib IB.

A clinical DDI study in healthy subjects using the index CYP3A substrate midazolam indicated that trilaciclib had no impact on CYP3A activity and that the strong CYP3A inducer rifampin had no clinically meaningful effect on trilaciclib PK. Two clinical DDI studies using a strong CYP3A inhibitor itraconazole were also conducted. No clinically significant changes in exposure were observed for trilaciclib when co-administered with itraconazole.

Gemcitabine has not been reported to be a substrate for MATE1 or MATE2 (Blackhall, 2010; Shen, 2013), and is not believed to be a substrate for OCT2. Carboplatin has not been reported to be a substrate for OCT2, MATE1, or MATE2 (Yonezawa, 2006). As such, based on a previous clinical trial with gemcitabine/carboplatin and trilaciclib (Study G1T28-04), gemcitabine/carboplatin administration following trilaciclib administration had no effect on trilaciclib PK and trilaciclib administered prior to chemotherapy had little to no effect on the PK of carboplatin or gemcitabine (for more detailed information, please refer to the trilaciclib IB).

Cisplatin has been reported to be a substrate of OCT2, MATE1 and MATE2-K (Wagner, 2016) and as such has the potential for DDI with trilaciclib, the net effect of which is difficult to predict due to the multiple drug transporters involved. Therefore, blood samples for the assessment of cisplatin PK will be collected in this study and signs of nephrotoxicity will be closely monitored.

In an additional clinical DDI assessment in healthy subjects, trilaciclib increased metformin (MATE1, MATE2-K and OCT2 substrate) exposure by 65% compared with administration of metformin alone. Avoid concomitant use of trilaciclib with certain OCT2, MATE1, and MATE2-K substrates (e.g., dofetilide, dalfampridine) where minimal concentration changes may lead to serious or life-threatening toxicities. Refer to the prescribing information for these concomitant medications for assessing the benefit and risk of concomitant use of trilaciclib.

4.5.3. Risks

4.5.3.1. Trilaciclib

Reproductive/embryo-fetal effects are an important potential risk of trilaciclib. Both nonclinical toxicology studies with trilaciclib, and clinical studies with other compounds with a similar MOA, report effects on either the reproductive system or embryo/fetus. Since this clinical study will focus on trilaciclib administered prior to cytotoxic chemotherapy and avelumab maintenance therapy (which carries their own risk of reproductive/embryo-fetal toxicity), the risks specific to trilaciclib are consistent with those experienced with chemotherapy and avelumab. In addition, female patients will be monitored for pregnancy and eligibility criteria describing specific birth control methods are incorporated. Dose discontinuation recommendations for female patients who become pregnant while receiving trilaciclib are also provided in the protocol (Section 11.3.6.5). Detailed information regarding all important identified and important potential risks of trilaciclib administration can be found in the trilaciclib IB.

At the clinical dose of 240 mg/m^2 being used in this study, trilaciclib did not have a clinically relevant effect on QTc (i.e., >10 msec).

In an integrated safety analysis from the four Phase 2 oncology studies conducted with trilaciclib to date (G1T28-02 [complete], G1T28-03 [data cutoff: 31 May 2019], G1T28-05 [data cutoff: 28 Jun 2019], and G1T28-04 [complete]), the most common TEAEs (≥10%) that occurred more frequently in patients receiving trilaciclib compared to placebo were nausea, fatigue, headache, dyspnea, cough, hypokalemia, and infusion related reaction. Trilaciclib-related TEAEs occurring in ≥5% of patients with at least a ≥2% higher incidence in trilaciclib compared to placebo were nausea, fatigue, anemia, headache, infusion related reaction, neutrophil count decreased, decreased appetite, vomiting, and constipation.

Adverse events of special interest (AESIs) identified for trilaciclib in the integrated safety summary are described below. Some AESIs have been infrequently reported (or not reported) in the trilaciclib clinical program to date but are considered to be potential class effects of CDK4/6 inhibitors. However, as trilaciclib is given IV and only when chemotherapy is administered, the safety profile of trilaciclib appears to be different from that of the oral, chronically-dosed members of its pharmacologic class. All patients will be monitored for these events and dose modification and discontinuation guidelines are provided in Section 9.3.

Trilaciclib AESIs:

1. **Injection Site Reaction/Phlebitis/Thrombophlebitis:** Infusion of trilaciclib can cause injection-site reactions including phlebitis and thrombophlebitis. Injection-site reactions including phlebitis and thrombophlebitis occurred in 56 (21%) of 272 patients receiving trilaciclib in clinical trials, including Grade 2 (10%) and Grade 3 (0.4%) AEs. The median time to onset from start of trilaciclib was 15 days (range 1 to 542) and from the preceding dose of trilaciclib was 1 day (1 to 15).The median duration was 1 day (range 1 to 151 for the resolved cases). Injection-site reactions including phlebitis and thrombophlebitis resolved in 49 (88%) of the 56 patients and led to discontinuation of treatment in 3 (1%) of the 272 patients.

   Monitor patients for signs and symptoms of injection-site reactions, phlebitis, and thrombophlebitis, including infusion-site pain and erythema during infusion. For mild

(Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue trilaciclib.

2. **Acute Drug Hypersensitivity Reaction:** Trilaciclib can cause acute drug hypersensitivity reactions, including facial edema and urticaria. Acute drug hypersensitivity reactions occurred in 16 (6%) of 272 patients receiving trilaciclib in clinical trials, including Grade 2 reactions (2%). One patient experienced a Grade 2 anaphylactic reaction 4 days after receiving trilaciclib, which resolved with epinephrine, and treatment with trilaciclib was continued. The median time to onset from start of trilaciclib was 77 days (range 2 to 256) and from the preceding dose of trilaciclib was 1 day (range 1 to 28). The median duration was 6 days (range 1 to 69 for the resolved cases). Acute drug hypersensitivity reactions resolved in 12 (75%) of the 16 patients.

   Monitor patients for signs and symptoms of acute drug hypersensitivity reactions including facial, eye, and tongue edema, urticaria, pruritus, and anaphylactic reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold trilaciclib until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue trilaciclib.

3. **Pneumonitis/Interstitial Lung Disease**: Severe, life-threatening, or fatal interstitial lung disease and/or pneumonitis can occur in patients treated with CDK4/6 inhibitors, the same drug class as trilaciclib. Interstitial lung disease /pneumonitis occurred in 1 (0.4%) of 272 patients receiving trilaciclib in clinical trials. The event was Grade 3 and reported 2 months after discontinuing trilaciclib, in a patient receiving a confounding medication. The event did not resolve.

   Monitor patients for pulmonary symptoms indicative of interstitial lung disease/pneumonitis such as cough, dyspnea, and hypoxia. For recurrent moderate (Grade 2) interstitial lung disease/pneumonitis, permanently discontinue trilaciclib. For severe (Grade 3) or life-threatening (Grade 4) interstitial lung disease/pneumonitis, permanently discontinue trilaciclib.

4. **Hepatotoxicity:** Both nonclinical toxicology studies with trilaciclib, and clinical studies with other compounds with a similar MOA, report reversible elevations in transaminases with continuous dosing. There has been only 1 instance of Grade 4 alanine aminotransferase (ALT) increase in a patient receiving trilaciclib, no Grade 4 aspartate aminotransferase (AST) increases, and no cases of Hy's law reported in patients receiving trilaciclib. However, generally low grade and transient increases in AST, ALT, or bilirubin have been observed in a small number of patients (~ 5%) receiving trilaciclib prior to chemotherapy. Patients with mild hepatic impairment have been treated with trilaciclib without a clinically significant increase in exposure or the frequency/severity of AEs.

5. **Embolic and Thrombotic Events, Venous:** The CDK4/6 inhibitor abemaciclib has been associated with an increased risk for venous thromboembolism when combined with endocrine therapy in patients with breast cancer. This same risk has not been reported for

the other approved oral CDK4/6 inhibitors (ribociclib and palbociclib); therefore it is not clear if this is a class effect. Approximately 3% of cancer patients that received trilaciclib prior to chemotherapy experienced a venous thromboembolic event and half of those events (3/6) were Grade 3 or 4. No Grade 5 events were reported. Approximately 2% of patients receiving chemotherapy alone or with placebo reported an embolic or thrombotic event, 1 of 3 such events was Grade 3.

4.5.3.2. Gemcitabine/Carboplatin/Cisplatin

4.5.3.2.1. Gemcitabine

Per Warnings and Precautions in the prescribing information/summary of product characteristics for gemcitabine (Gemzar®, 2019 [US]; Gemzar, 2019 [EU]), the following are important risks related to gemcitabine use:

- Bone marrow suppression: neutropenia, thrombocytopenia, and anemia, including Grade 3 or 4 hematologic toxicity
- Capillary leak syndrome
- Hemolytic uremic syndrome: may lead to renal failure and dialysis (including fatalities).
- Hepatotoxicity
- Hypersensitivity: Anaphylaxis and allergic reactions (including bronchospasm and anaphylactoid reactions) have been observed
- Posterior reversible encephalopathy syndrome: may manifest with blindness, confusion, headache, hypertension, lethargy, seizure, and other visual and neurologic disturbances
- Pulmonary toxicity: including adult respiratory distress syndrome, interstitial pneumonitis, pulmonary edema, and pulmonary fibrosis

4.5.3.2.2. Carboplatin

Per Warnings and Precautions in the prescribing information/summary of product characteristics for carboplatin (Carboplatin, 2020 [EU]; Carboplatin, 2018 [US]), the following are important risks related to carboplatin use:

- Bone marrow suppression: leukopenia, neutropenia, and thrombocytopenia
- Nephrotoxic potential: concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity
- Emesis
- Peripheral neurotoxicity: observed infrequently, but its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin
- Loss of vision
- Allergic reactions, including anaphylaxis

- Abnormal liver function tests
- Fetal harm

4.5.3.2.3. Cisplatin

Per Warnings and Precautions in the prescribing information/summary of product characteristics for cisplatin (Cisplatin, 2020 [EU]; Cisplatin, 2019 [US]), the following are important risks related to cisplatin use:

- Hypersensitivity reactions: anaphylaxis and death may occur
- Ototoxicity: cumulative toxicity may be severe
- Ocular toxicity: optic neuritis, papilledema, and cortical blindness may occur
- Nephrotoxicity
- Secondary acute leukemia
- Fetal harm

Trilaciclib may increase cisplatin exposure in some patients.

4.5.3.2.4. Avelumab

Per Warnings and Precautions in the prescribing information/summary of product characteristics for avelumab (Bavencio, 2020 [US]; Bavencio, 2020 [EU]), the following are important risks related to avelumab use:

- Immune-mediated adverse reactions: may be severe or fatal, can occur in any organ system or tissue, including immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies (type I diabetes mellitus which can present with diabetic ketoacidosis, thyroiditis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis), dermatologic adverse reactions, nephritis and renal dysfunction, and solid organ transplant rejection.
- Infusion-related reactions
- Complications with allogeneic hematopoietic stem cell transplant: fatal and other serious complications can occur in patients who receive hematopoietic stem cell transplant before or after being treated with a PD-1/PD-L1-blocking antibody
- Fetal harm

Any AE that is suspected to be a potential immune-related AE is considered an avelumab AESI. Refer to the avelumab prescribing information/summary of product characteristics for a detailed description of anticipated safety risks for avelumab and their management (Bavencio, 2020 [US]; Bavencio, 2020 [EU]).

4.6. Benefit/Risk Assessment

Trilaciclib (a CDK4/6 inhibitor) is being evaluated for anti-tumor efficacy as well as its ability to improve the patient experience while receiving chemotherapy. In addition to the side effects of chemotherapy, chemotherapy-induced immunosuppression may limit anti-tumor efficacy due to

an inability of the host immune system to effectively mount a response against the cancer. Therefore, administration of trilaciclib to preserve the bone marrow and the immune system from the cytotoxic effects of chemotherapy has the potential to maximize anti-tumor activity of the chemotherapy. As stated in Section 4.5.2, the dose of 240 mg/m^2 trilaciclib established in Phase 1b/2a SCLC studies and in the Phase 2 TNBC study, will be used in this study and administered prior to a commonly used platinum-based chemotherapy regimen and maintenance regimen; a dose that has shown efficacy in myeloprotection (in SCLC studies) as well as in survival outcomes (TNBC).

Studies to date with trilaciclib have demonstrated a manageable safety profile (see Section 4.5.3.1). In Study G1T28-04, the rates of overall toxicity were comparable in TNBC patients who received trilaciclib with gemcitabine/carboplatin versus gemcitabine/carboplatin alone despite the 2-fold increase in the median number of cycles and 50% increase in the cumulative dose of both gemcitabine and carboplatin in patients who received trilaciclib. Rates of discontinuation due to an AE were not different between the trilaciclib groups and the gemcitabine/carboplatin alone group. Similarly, in patients with SCLC administered trilaciclib with etoposide/carboplatin/atezolizumab (E/P/A) in Study G1T28-05, the rates of overall toxicity profile were comparable in patients who received trilaciclib plus E/P/A versus placebo plus E/P/A despite the lower relative dose intensity of E/P/A being lower in patients in the placebo group compared with the trilaciclib group, with the trilaciclib group having fewer having a lower number of dose delays/reduction. In addition, patients receiving trilaciclib had lower rates of discontinuation due to an AE and atezolizumab AEs of special interest as compared with patients receiving placebo. In conclusion, combination treatment with trilaciclib and platinum-based chemotherapy and ICI maintenance therapy offers the potential for clinical benefit with a favorable safety profile.

A COVID-19 risk assessment has been performed, documented, and will be provided as a separate document.

5. OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives of this study in patients treated with platinum-based chemotherapy and avelumab maintenance therapy for untreated locally advanced or metastatic urothelial carcinoma, and their associated endpoints, are presented in Table 4.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To evaluate the anti-tumor efficacy of trilaciclib compared to a control group	• PFS during the overall study
Secondary Objectives: Efficacy	
• To evaluate the anti-tumor efficacy of trilaciclib compared to a control group	• ORR defined as the proportion of patients who had an objective response (unconfirmed or confirmed) per RECIST v1.1 (chemotherapy period, maintenance period, during the overall study) • DCR defined as the proportion of patients with best overall response of confirmed CR or PR, or SD per RECIST v1.1 (maintenance period, during the overall study) • DOR per RECIST v1.1 (during the overall study) • PFS (maintenance period) • Probability of survival at Month 16 • OS (maintenance period, during the overall study)
To evaluate the myeloprotective effects of trilaciclib when combined with platinum-based chemotherapy compared with chemotherapy alone	
• To assess the effects of trilaciclib on the neutrophil lineage compared to a control group	• Duration of severe (Grade 4) neutropenia in Cycle 1 • Occurrence of severe (Grade 4) neutropenia • Occurrence of febrile neutropenia AEs • Occurrence of G-CSF administration
• To assess the effects of trilaciclib on the RBC lineage compared to a control group	• Occurrence of Grade 3 or 4 decreased hemoglobin laboratory values • RBC transfusions on or after Week 5 (occurrence and number of transfusions) • Occurrence of ESA administration

Objectives	Endpoints
• To assess the effects of trilaciclib on the platelet lineage compared to a control group	• Occurrence of Grade 3 or 4 decreased platelet count laboratory values • Platelet transfusions (occurrence and number of transfusions)
• To assess the effects of trilaciclib on hospitalizations due to chemotherapy-induced myelosuppression compared to a control group	• Occurrence and number of hospitalizations due to chemotherapy-induced myelosuppression
• To assess the effects of trilaciclib on chemotherapy dosing compared to a control group	• All-cause dose reductions (occurrence and number of reductions) • All-cause cycle delays (occurrence and number of delays)
Secondary Objectives: Safety	
• To assess the safety and tolerability of trilaciclib compared to a control group	• Occurrence and severity of AEs by NCI-CTCAE v5.0 • Trilaciclib AESIs • Avelumab AESIs • Changes in laboratory parameters (hematology and serum chemistry), vital signs and ECG parameters • Grade 3 or 4 abnormalities in serum chemistry laboratory parameters • Occurrence of trilaciclib dose delays and infusion interruptions • Occurrence of chemotherapy dose reductions • Occurrence of chemotherapy dose delays and infusion interruptions • Occurrence of avelumab dose delays and infusion interruptions
Exploratory Objectives	
• To assess the pharmacodynamic effects, including immune-based mechanism, of trilaciclib when added to platinum-based chemotherapy and avelumab therapy in tumor biopsies and peripheral blood	• Differences in pharmacodynamic parameters, including those relating to immune-based mechanisms, in tumor and peripheral blood

Objectives	Endpoints
• To understand the effect of trilaciclib in CDK4/6-dependent tumors when added to platinum-based chemotherapy and avelumab maintenance therapy	• PFS, OS, and ORR (per RECIST v1.1) during the study in patients with each of the following CDK4/6 dependence signatures: – CDK4/6 dependent – CDK4/6 independent – CDK4/6 indeterminant
• To assess the effects of trilaciclib on PFS, OS, ORR, DOR, and DCR in the PD-L1 subgroups	• PFS, OS, ORR, DOR and DCR during the study in PD-L1 subgroups (as measured by retrospective analysis)
• To assess the PK of trilaciclib and metabolites, cisplatin, and avelumab when trilaciclib is administered with either cisplatin or avelumab	• PK parameters as data permit
• To assess the immunogenicity of avelumab when administered with trilaciclib	• Anti-avelumab antibodies • Neutralizing antibodies

AE=adverse event; AESI=adverse event of special interest; CDK=cyclin-dependent kinase; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; DCR=disease control rate; DOR=duration of response; ECG=electrocardiogram; ESA=erythropoiesis stimulating agent; G-CSF=granulocyte colony-stimulating factor; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression free survival; PK=pharmacokinetic; PR=partial response; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an exploratory Phase 2, multicenter, randomized, open-label study evaluating the safety and efficacy of trilaciclib administered with platinum-based chemotherapy followed by trilaciclib administered with avelumab maintenance therapy compared with platinum-based chemotherapy followed by avelumab maintenance therapy in patients receiving first-line treatment for advanced/metastatic urothelial carcinoma. Inclusion/exclusion criteria are outlined in Section 7.1 and Section 7.2, respectively.

Approximately 90 patients will be randomly assigned (1:1) to one of two treatment arms:

- Arm A – platinum-based chemotherapy followed by avelumab maintenance therapy
- Arm B – trilaciclib plus platinum-based chemotherapy followed by trilaciclib plus avelumab maintenance therapy

Platinum-based chemotherapy (with or without trilaciclib) will be administered IV in 21-day cycles, and avelumab maintenance therapy (with or without trilaciclib) will be administered IV in 14-day cycles. There will be two stratification factors for randomization: presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin).

Common Design Features for All Treatment Arms

Study drugs will be administered as follows:

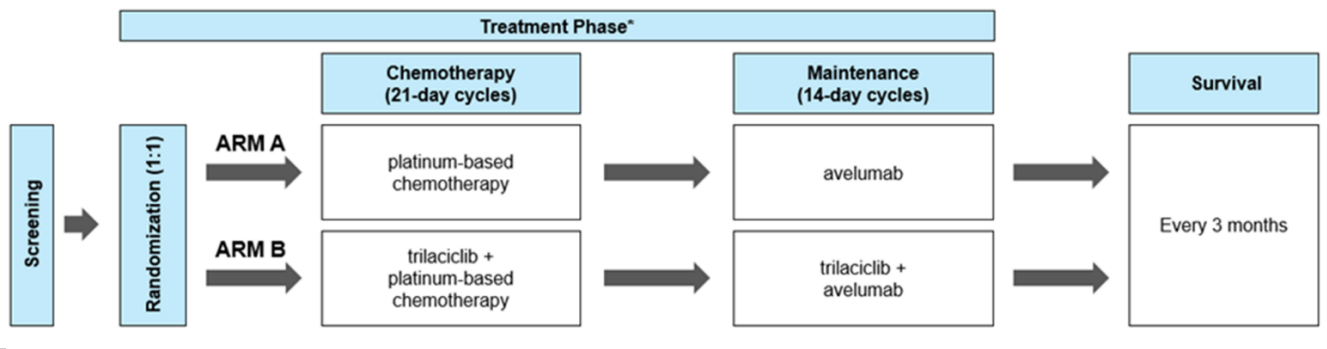
- Gemcitabine 1000 mg/m^2 administered IV on Day 1 and Day 8 of each 21-day chemotherapy cycle.
- Cisplatin eligible: cisplatin 70 mg/m^2 administered IV on Day 1 of each 21-day chemotherapy cycle. Split dosing on Day 1 and Day 8 is permitted for toxicity management as described in Section 9.3.1.1. Gemcitabine should be administered prior to cisplatin.
- Cisplatin ineligible: carboplatin using Calvert formula with a target area under the curve (AUC) = 4.5 administered IV on Day 1 of each 21-day chemotherapy cycle. Gemcitabine should be administered prior to carboplatin.
- Other platinum-based chemotherapies, such as methotrexate/carboplatin/vinblastine (M-CAVI) for example, are not permitted in this study.
- Avelumab 800 mg administered IV on Day 1 of each 14-day maintenance cycle as a 60-minute infusion. In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory for the first 4 infusions (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate. Premedication should be administered for subsequent

avelumab doses based upon clinical judgment and presence/severity or prior infusion reactions.

- Trilaciclib 240 mg/m^2 administered as a 30-minute IV infusion completed within 4 hours prior to the start of platinum-based chemotherapy (Day 1 and Day 8) or avelumab maintenance therapy (Day 1)

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase (Figure 5). The Treatment Phase begins on the day of randomization and completes at the End of Treatment Visit. Survival Follow-up assessments should occur every 3 months after the End of Treatment Visit (including assessments at Month 17 Day 1.

Figure 5: Study Schema



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

Patients enrolled in the study will be eligible to receive 4-6 cycles of platinum-based chemotherapy, per Investigator's discretion. Patients without progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (i.e., with an ongoing complete response [CR], partial response [PR], or stable disease [SD]) after platinum-based chemotherapy will be eligible to receive avelumab maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first. Treatment visits will occur consecutively as planned without interruption, except when necessary to manage toxicities or for administrative reasons (long weekends, holidays, weather conditions, etc.). There should be no more than 42 days between the start of each platinum-based chemotherapy cycle (with or without trilaciclib). Dosing delays >42 days between the start of each platinum-based chemotherapy cycle may be permitted on a case-by-case basis with the approval of the Investigator and Medical Monitor. There should be no more than 56 days between doses of avelumab maintenance therapy (with or without trilaciclib). Dosing delays >56 days between doses of avelumab maintenance therapy may be permitted on a case-by-case basis with the approval of the Investigator and Medical Monitor. Avelumab maintenance therapy (with or without trilaciclib) should begin at a minimum of 4 and not more than 10 weeks after the last dose of platinum-based chemotherapy (with or without trilaciclib).

Criteria which patients must meet in order to receive study drug on Day 1 and on Day 8 during chemotherapy treatment are provided in Section 9.2.

An End of Treatment Visit will occur approximately 14 days following a patient's last dose of study drug. Safety Follow-up visits (which may be a phone call) will occur 30 days after their last dose of study drug and 90 days after the last dose of avelumab. Patients will be followed for survival approximately every 3 months (including and assessment at Month 17 Day 1) after the End of Treatment Visit. Survival Follow-up Visits may be done via telephone, email, or clinic visit. Patients will be followed for survival, at a minimum, until at least 60% of patients in the study have died, or the end of study, whichever occurs first.

A Data Monitoring Committee (DMC) will monitor accumulating safety and anti-tumor response data with the first meeting planned when approximately10 patients treated with trilaciclib + cisplatin or 10 patients treated with trilaciclib + carboplatin have completed at least 2 cycles, whichever occurs first. The meetings will continue approximately every 6 months or as defined in the DMC charter while patients are on study treatment depending upon the enrollment rate. Additional reviews may occur. For more information, refer to Section 11.7.

The study will be completed when the criteria outlined in Section 10.4 have been met or upon sponsor termination of the study.

6.2. Rationale for Primary and Secondary Endpoints

6.2.1. Anti-tumor Efficacy

Measurements of anti-tumor efficacy as measured by probability of survival, OS and PFS, as well as anti-tumor response rates by RECIST v1.1, ORR, disease control rate (DCR), and duration of response (DOR), are standard assessments used in oncology solid tumor studies to measure the effects of study treatment on the underlying malignant disease. Additionally, clinical benefit in oncology should be based on direct evidence, such as improvement in duration of OS, improvement in a patient's quality of life, improved physical functioning, or improved tumor related- symptoms, which may not be adequately measured by response rates alone. Therefore, improvement in survival is considered one of the most reliable measures in providing direct evidence of clinical benefit to patients and is a preferred clinical endpoint. Survival is considered easy to measure via documentation of the date of death and is not prone to bias (FDA, 2008).

6.2.2. Myeloprotection Efficacy

Patients experiencing chemotherapy-induced myelosuppression often face severe clinical consequences (e.g., febrile neutropenia [FN] predisposes patients to serious infections and even death). For those patients with neutropenia requiring hospitalization, the estimated inpatient mortality rates ranged from 3.4% to 10.5% depending on tumor type in 1 study, with an overall mortality rate of 6.8% (Caggiano, 2005). In another analysis, the overall rate of death was 9.5%, with rates for solid tumor cancer patients ranging from 3.6% for breast cancer patients to 13.4% for lung cancer patients (Kuderer, 2006). Because both the severity and duration of neutropenia correlate with the risk of FN and infections (Bodey, 1966; Gustinetti, 2016; Li, 2016), a reduction in its occurrence and duration will decrease the risk of these events and provide an improved patient experience while receiving chemotherapy (Padilla, 2005). The measurement of DSN is limited to Cycle 1 because the risk of FN is highest in Cycle 1 (Culakova, 2014) and because the data collected in Cycle 1 in this study will not be subject to bias due to granulocyte

colony-stimulating factor (G-CSF) administration since primary prophylactic G-CSF will be prohibited in Cycle 1.

6.2.3. Safety

Assessment of AEs, changes in laboratory parameters, vital signs, and ECOG performance status are all standard assessments used in oncology trials to measure patient safety.

6.3. Rationale for Dose and Schedule of Study Treatment

Previous studies demonstrated the RP2D of trilaciclib was 240 mg/m^2. When trilaciclib was administered prior to chemotherapy to cancer patients, doses of 200 (rounded up from 192), 240, and 280 mg/m^2 were evaluated. Trilaciclib exposures in cancer patients were slightly lower compared with healthy subjects, such that the dose of 240 mg/m^2 (rather than 200 mg/m^2) more closely matched the biologically effective dose of 192 mg/m^2. In addition, the dose of 240 mg/m^2 demonstrated maximal myeloprotection efficacy benefits (compared with 200 and 280 mg/m^2) as measured by a variety of myelosuppression endpoints. The myeloprotective effect at 240 mg/m^2 was further evaluated and confirmed in three randomized controlled Phase 2 studies in SCLC patients. In addition, both the planned schedule and the planned doses of trilaciclib, gemcitabine, and carboplatin were used in the previous TNBC study (G1T28-04) and demonstrated clinically meaningful benefits in OS duration. See the trilaciclib IB for details. The dose and schedule for avelumab maintenance therapy follows the instructions located in the local prescribing information/summary of product characteristics.

6.4. Rationale for Patient Population

Inoperable locally-advanced/metastatic urothelial carcinoma is a uniformly lethal disease with high unmet medical need. Platinum-based chemotherapy is the current standard of care for patients with previously untreated metastatic urothelial carcinoma. Systemic chemotherapy in metastatic urothelial carcinoma is, however, characterized by significant toxicity with poor OS and low response rates and limited durability in a frail population of advancing age and multiple co-morbidities.

Many first-line patients are medically unfit or ineligible to receive treatment with cisplatin-based chemotherapy (cis-ineligible) and need more effective therapeutic options. For patients who are deemed ineligible to receive cisplatin, treatment options include carboplatin-based or non-platinum-based combinations and best supportive care. For patients who do not receive chemotherapy, the outcomes remain extremely poor. The addition of trilaciclib to platinum-based chemotherapy and avelumab maintenance therapy could provide a meaningful treatment option for patients receiving first-line treatment.

6.5. Rationale for Platinum-Based Chemotherapy and Avelumab Therapy

In accordance with treatment guidelines, patients with previously untreated urothelial carcinoma typically receive platinum-based chemotherapy such as gemcitabine and cisplatin or gemcitabine and carboplatin. Participation in clinical studies of new or more-tolerable therapy is also recommended (NCCN, 2020).

The efficacy of platinum-based chemotherapy in treating urothelial carcinoma may be due to the capacity to stimulate an immune response (Zitvogel, 2008). Gemcitabine chemotherapy has been shown to reduce MDSCs in murine mouse models and lead to more effective anti-cancer immunity (Suzuki, 2005; Ko, 2007; Le, 2009; Sawant, 2013). While MDSCs have been described in both the blood and tumors of patients with urothelial carcinoma, the role they play remains unclear (Eruslanov, 2012). Gemcitabine may also have beneficial immune effects mediated through depletion of regulatory T cells in selected animal models (Shevchenko, 2013). In a nonclinical study, cisplatin enhanced tumor cell susceptibility to cytotoxic T cell-mediated killing (Ramakrishnan, 2010).

The benefit of carboplatin-based therapy in cisplatin-ineligible patients was demonstrated in the EORTC Trial 30986. In this study, 238 patients with previously untreated advanced urothelial carcinoma and either a poor performance status and/or impaired renal function (glomerular filtration rate [GFR] <60 but >30 mL/min) were enrolled to receive gemcitabine/carboplatin or M-CAVI (De Santis, 2012). The confirmed ORR of gemcitabine/carboplatin was 36.1% versus 21.0% for the M-CAVI arm. However, there was no evidence of a difference in OS (HR=0.94; 95% CI: 0.72, 1.22; p=0.64); median OS was 9.3 and 8.1 months, respectively.

Immunotherapy in urothelial carcinoma has shown significant promise (Galsky, 2020; Powles, 2020). Tumor-cell killing by cytotoxic chemotherapy alone can be expected to expose the immune system to high levels of tumor antigens; invigorating tumor-specific T cell immunity in this setting by inhibiting PD-L1/PD-1 signaling and by using the combination of avelumab and chemotherapy may result in deeper and more durable responses compared with standard chemotherapy alone.

Treatment with avelumab in treatment-resistant urothelial carcinoma has shown responses in patients with platinum-refractory cancer and has received approval from the US FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Bavencio, 2020). Patients enrolled in the Phase 1b JAVELIN Solid Tumor study with previously treated advanced/metastatic urothelial carcinoma received avelumab 10 mg/kg every 2 weeks until disease progression. The ORR in all patients was 16.5% (CR in 4.1% and PR in 12.5%), with a median DOR of 20.5 months. Median PFS was 1.6 months with a 12-month PFS rate of 16.8%, and median OS was 7.0 months with a 24-month OS rate of 20.1%. Avelumab also showed antitumor activity in high-risk subgroups, including elderly patients and those with renal insufficiency or upper tract disease (Apolo, 2020).

Treatment with avelumab has also shown responses as a maintenance treatment in patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy and has received approval from the US FDA (Bavencio, 2020) and a positive opinion from the European Committee for Medicinal Products for Human Use (European Medicines Agency, 2020) and approval by the European Commission. In the pivotal Phase 3 JAVELIN Bladder 100 study, patients with unresectable locally advanced or metastatic urothelial carcinoma who did not have disease progression after 4-6 cycles of platinum-based chemotherapy were randomly assigned to receive best supportive care (control) or best supportive care with avelumab 10 mg/kg administered every 2 weeks until disease progression. Median OS in the avelumab group versus the control group was 21.4 months versus

14.3 months (HR=0.69, p=0.001), with OS at 1 year of 71.3% in the avelumab group and 58.4% in the control group. Median PFS in the avelumab group versus control group was 3.7 months versus 2.0 months (HR=0.62). Disease control rates (defined as a best overall response of CR, PR, SD, or non–CR or non–progressive disease) was 41.1% in the avelumab group and 27.4% in the control group (Powles, 2020). Based on local prescribing guidelines, this study will use the flat dose of 800 mg.

The addition of trilaciclib to platinum-based chemotherapy and avelumab maintenance therapy may offer the potential for clinical benefit and a manageable tolerability profile in patients with metastatic urothelial carcinoma receiving first-line treatment.

6.6. Rationale for Supportive Care Interventions (Growth Factors and Transfusions)

In order to facilitate an unbiased evaluation of trilaciclib effects on the hematologic and pharmacodynamic endpoints, primary prophylactic G-CSF will be prohibited in Cycle 1; however therapeutic G-CSF (administered in response to a neutropenic event) in Cycle 1 and secondary prophylactic G-CSF 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 in Section 9.4.1 and Investigator discretion (Aapro, 2011; Smith, 2015).

Erythropoiesis-stimulating agent (ESA) administration and RBC or platelet transfusions will be allowed per Investigator discretion based on guidelines detailed in Section 9.4.2 and Section 9.4.3. While these interventions may confound analysis of the myelosuppression endpoints, allowing physicians to provide appropriate supportive care to patients will facilitate patient safety.

6.7. Rationale for Stratification Factors

As outlined in Section 6.1, randomization of patients will be stratified by two stratification factors: presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin). These stratification factors were chosen because they are predicted to have an impact on study endpoints such that if there is an imbalance in this factor, interpretation of the results of the study could be compromised. In a Phase 3 study in second-line urothelial carcinoma comparing vinflunine with best supportive care and which examined 16 potential prognostic factors for their association with survival, patients with visceral involvement had the worst OS outcome (Bellmunt, 2009). In a separate study, liver metastasis was a disease factor included in a model that showed prognostic performance for survival across three PD-L1 inhibitors to treat metastatic urothelial carcinoma after platinum-based chemotherapy (Sonpavde, 2020). Finally, multiple studies have shown differences in survival outcomes in patients with urothelial carcinoma administered cisplatin versus carboplatin treatment (Powles, 2020; Galsky, 2020; Galsky, 2012).

7. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

7.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriately qualified member of the investigator study team before patients are included in the study. Patients must meet *all* of the following inclusion criteria to be eligible for enrollment into the study:

1. Age ≥18 years
2. Histologically documented, locally advanced (T4b, any N; or any T, N 2-3) or metastatic urothelial carcinoma (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)
    a. Patients with mixed histologies are required to have a dominant transitional cell pattern (small cell carcinoma of any proportion is not allowed)
    b. Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2-N3)
3. Measurable disease as defined by RECIST v1.1
    a. Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy and no other lesions are available for selection as target lesions.
4. Considered to be eligible to receive platinum-based chemotherapy and avelumab maintenance therapy, in the Investigator's judgment
5. No prior systemic therapy in the inoperable, locally advanced, or metastatic setting including chemotherapy, immune checkpoint inhibitor therapy, targeted therapy, or investigational agents
    a. For patients who received prior adjuvant/neoadjuvant chemotherapy for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting. If a patient received adjuvant/neoadjuvant chemoradiation for urothelial carcinoma, a treatment-free interval >12 months between last platinum dose and the date of recurrence is required.
    b. For patients who received prior ICI therapy in the adjuvant/neoadjuvant setting, a treatment-free interval > 3 months between the last dose of ICI and date of recurrence is required.
    c. Prior local intravesical chemotherapy or immunotherapy is allowed if completed ≥4 weeks prior to the initiation of study treatment
6. A formalin-fixed paraffin-embedded (FFPE) tumor tissue block (75-micron) or at least 15 (5-micron) unstained slides from archival or fresh tumor biopsy or resection; the most recent biopsy tissue preferred. Patients who have fewer than 15 unstained slides available

at baseline (but no fewer than 10) may be eligible following discussion with the Medical Monitor.

a. Tumor tissue should be of good quality based on total and viable tumor content. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
b. Transurethral resection of bladder tumor (TURBT) specimens must contain a muscle -invasive component (i.e., T2 or greater) of the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle-invasive component, then specimens obtained at the time of cystectomy/nephroureterectomy (i.e., pT2 or greater) or metastatic spread (i.e., a sample from a metastatic lesion) will be required prior to randomization. An archival specimen, if available, should also be submitted.
c. Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
d. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

7. ECOG performance status of 0-2
8. Adequate organ function as demonstrated by the following laboratory values:
    a. Hemoglobin ≥9.0 g/dL in the absence of RBC transfusion or ESA administration within 14 days prior to first dose of study drug
    b. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    c. Platelet count $\geq 100 \times 10^9$/L
    d. Estimated glomerular filtration rate ≥ 30 mL/minute/1.73 m^2
    e. Total bilirubin ≤1.5 × upper limit of normal (ULN) (<3 ULN if Gilbert's disease)
    f. ALT and AST ≤2.5 × ULN in the absence of liver metastasis or <5 × ULN in the presence of liver metastasis
9. Resolution of nonhematologic toxicities from prior systemic therapy, radiation therapy, or surgical procedures to ≤ Grade 1
    a. Alopecia and sensory neuropathy ≤ Grade 2, as well as any electrolyte laboratory abnormalities not constituting a safety risk based on investigator's judgment are acceptable
10. Predicted life expectancy of ≥3 months
11. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Please see Section 17.3 for detailed instructions on methods of contraception requirements.
12. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

7.2. Exclusion Criteria

A patient will not be eligible for participation in this study if *any* of the following criteria apply:

1. Prior treatment with IL-2, IFN-α, anti-PD-L2, anti-CD137 or CD137 agonists, or cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibody (including ipilimumab), or any other therapeutic antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways in any setting within 12 months prior to randomization
2. Malignancies other than urothelial carcinoma within 2 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ, or low-grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (e.g., surgery, radiation, or castration), or other non-clinically significant cancers, which may be considered after discussion with the medical monitor
3. Presence of central nervous system (CNS) metastases/leptomeningeal disease requiring immediate treatment with radiation therapy or steroids. Patient must be off steroids administered for brain metastases for at least 2 weeks prior to the first dose of study drugs. No stereotactic radiation within 1 week or whole-brain radiation within 14 days prior to first dose of study drugs
4. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (≥ Class II New York Heart Association functional classification system), myocardial infarction within 6 months prior to first dose of study drugs, unstable angina, or serious cardiac arrhythmia requiring medication
5. QTcF interval > 480 msec. For patients with ventricular pacemakers, QTcF > 500 msec
6. Known history of stroke or cerebrovascular accident within 6 months prior to first dose of study drugs
7. Known history of serious, chronic active infection (e.g., human immunodeficiency virus, hepatitis B or C, tuberculosis, etc.)
    a. Viral load indicative of HIV, HIV 1/2 antibodies, positive hepatitis B virus surface antigen or hepatitis C virus ribonucleic acid (RNA) if anti-hepatitis C virus antibody screening test positive
8. Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
    a. Therapeutic oral or IV antibiotic use within 2 weeks prior to randomization
    b. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease or for dental extraction) are eligible
9. Other uncontrolled serious chronic disease or psychiatric condition that in the Investigator's opinion could affect patient safety, compliance, or follow-up in the protocol
10. Receipt of any investigational medication within 4 weeks, or at least 5 half-lives, whichever is greater, prior to the first dose of study drugs
11. Known hypersensitivity or allergy to study drugs or any component in their formulations

12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more features of asthma symptom control per Global Initiative for Asthma [GINA] 2020) (GINA, 2020)
13. Prior hematopoietic stem cell or bone marrow transplantation, or solid organ transplantation
14. Radiotherapy to any non-CNS site within 1 week prior to the first dose of study drugs, or within 2 weeks to any CNS sites
15. Pregnant or lactating women
    a. Women of childbearing potential must have negative serum pregnancy test result within 7 days prior to initiating study treatment
16. Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to study treatment start, or anticipation of the need for major surgical procedure during the course of the study
17. Received a live, attenuated vaccine within 4 weeks prior to the first dose of study drugs
    a. Inactive vaccines, including but not limited to influenza vaccine, pneumococcal vaccine, shingles vaccine, and regionally approved Covid-19 vaccines are allowed
    b. Patients must agree not to receive a live, attenuated influenza vaccine during study treatment
18. History of immune colitis, inflammatory bowel disease, idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
    a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
19. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
20. Current use of immunosuppressive medication, EXCEPT for the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)
    b. Systemic corticosteroids at physiological doses ≤10 mg/day of prednisone or equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
21. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who are employees of G1 Therapeutics, Inc. directly involved in the conduct of the study.

8. SCHEDULE OF ASSESSMENTS

The procedures and assessments to be performed during the study are outlined in Table 5. The timing and number of samples collected for biomarker testing may be altered based on emerging data without requiring an amendment if the blood volume per day or overall does not increase and the patient is not required to have additional clinic visits or prolongation of a clinic visit, i.e., the risk-benefit profile for the patient does not worsen.

Unless otherwise specified, assessments are to be completed within ±1 day of the scheduled visit date. Unscheduled assessments and visits to manage patient safety may occur at the Investigator's discretion. Study procedures performed at unscheduled visits should be recorded in the appropriate electronic case report form (eCRF).

Table 5: Schedule of Assessments

	Study Treatment								Follow-Up			See Protocol Section
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up	
Assessment	**30 days prior to C1D1**	**Day 1 (±1d)**	**Day 2**	**Day 8 (±1d)**	**Day 13 and Day 17 (±1d)**	**Day 1 (±1d)**	**Day 2**	**14 days after last dose of study drug (±3d)**	**30 days after last dose of study drug (+7d)**	**90 days after last dose of avelumab (±7d)**	**Every 3 months after ETV (±7d) [a]**	
Informed Consent	X											Section 13.3
Randomization		X [C1 only (-7d)]										Section 11.1.2
Inclusion/Exclusion Criteria	X											Section 7
Demographics	X											Section 11.1.3
Medical History and Surgical History	X											Section 11.1.4
Archival and/or fresh FFPE tumor specimen or 15 unstained slides	X											Section 11.5.1
Concomitant Medications	X	X		X		X		X	X	X		Section 11.1.4
Complete Physical Examination	X											Section 11.3.2
Physical Examination when symptoms warrant per Investigator discretion		X				X		X				Section 11.3.2
Vital Signs	X	X		X		X		X				Section 11.3.1

Assessment	Study Treatment								Follow-Up			See Protocol Section
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up	
	30 days prior to C1D1	Day 1 (±1d)	Day 2	Day 8 (±1d)	Day 13 and Day 17 (±1d)	Day 1 (±1d)	Day 2	14 days after last dose of study drug (±3d)	30 days after last dose of study drug (+7d)	90 days after last dose of avelumab (±7d)	Every 3 months after ETV (±7d) [a]	
ECOG Performance Status	X	X				X [every-other cycle]		X				Section 11.3.3
AE Reporting		X										Section 11.3.6
Laboratory Assessments and Procedures												
Hematology	X	X	X [C1 only]	X	X [C1 only]	X		X	X			Section 11.3.5
Chemistry	X	X				X		X	X			Section 11.3.5
Free T4 and TSH	X					X [Q8 wk]		X				Section 11.3.5
Urinalysis (dipstick)	X							X				Section 11.3.5
Pregnancy Test (WOCBP only)	X	X				X [every-other cycle; C1 start]		X				Section 11.3.5
Anti-avelumab antibody and neutralizing antibody testing						X [C1, C3, C6 only]		X				Section 11.6
12-lead ECG	X											Section 11.3.4

Assessment	Study Treatment								Follow-Up			See Protocol Section
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up	
	30 days prior to C1D1	Day 1 (±1d)	Day 2	Day 8 (±1d)	Day 13 and Day 17 (±1d)	Day 1 (±1d)	Day 2	14 days after last dose of study drug (±3d)	30 days after last dose of study drug (+7d)	90 days after last dose of avelumab (±7d)	Every 3 months after ETV (±7d) [a]	
Blood samples for biomarkers		X [C1, C2, C3 only]		X [C1 only]		X [C1, C3 only]						Section 11.5.2
Blood samples for trilaciclib and metabolites PK (Arm B only)		X [C1 only]	X [C1 only]			X [C1, C3, only]	X [C1, C3, only]					Section 11.4
Blood samples for cisplatin PK (only patients treated with cisplatin)		X [C1 only]		X [C1 only]								Section 11.4
Blood samples for avelumab PK (Arm B only)						X [C1, C3, C6 only]						Section 11.4
Study Treatment												
Trilaciclib (Arm B only)		X		X		X						Section 9.1
gemcitabine		X		X								Section 9.1
cisplatin [b] or carboplatin		X		X [b]								Section 9.1
avelumab						X						Section 9.1

Assessment	Study Treatment								Follow-Up			See Protocol Section
	Screening	Chemotherapy Period (4-6 cycles; 1 cycle=21d)				Maintenance Period (1 cycle=14d)		End of Treatment Visit (ETV)	Safety Follow-up Visit		Survival Follow-Up	
	30 days prior to C1D1	Day 1 (±1d)	Day 2	Day 8 (±1d)	Day 13 and Day 17 (±1d)	Day 1 (±1d)	Day 2	14 days after last dose of study drug (±3d)	30 days after last dose of study drug (+7d)	90 days after last dose of avelumab (±7d)	Every 3 months after ETV (±7d) [a]	
Disease Assessment												
Tumor Assessments (CT/MRI)	X	CT/MRI of chest/abdomen/pelvis Q6 weeks (±7d) during the chemotherapy period and Q8 weeks (±7d) during the avelumab maintenance period for up to 1 year relative to Cycle 1 Day 1 and Q12 weeks (±7d) thereafter relative to Cycle 1 Day 1 until documented disease progression or subsequent anticancer therapy. Brain scan (MRI preferred) during screening is not required and should be performed per investigator discretion based on clinical signs and symptoms. Additional brain MRI should be conducted if there are brain metastases present at baseline or new clinical signs and symptoms suggestive of brain metastases. Bone metastases identified at baseline via a bone scan or PET (such as FDG-PET, NaF-PET, or other locally available PET options) to be followed at scheduled visits using localized CT or MRI as clinically indicated. If bone metastases cannot be seen on CT or MRI scans, bone scans, or PET should be repeated, using the same diagnostic procedure bone metastases were at baseline, when CR is identified in target disease or when progression in bone is suspected.										Section 11.2.1
Survival Follow-Up and Subsequent Anti-Cancer Treatments [a]											X	Section 11.10

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

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

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

9. STUDY TREATMENT

9.1. Study Drugs Administered

Study drugs are defined as any investigational product, chemotherapy, or other therapy intended to be administered to a study patient according to the study protocol. Study drugs used in this protocol are described in Table 6.

Table 6: Study Drugs

Name	Trilaciclib	Gemcitabine	Cisplatin or Carboplatin	Avelumab
Type	Investigational Product	Chemotherapy	Chemotherapy	PD-L1 inhibitor
Dose Formulation	Single-use, sterile powder to be reconstituted with 250 mL of dextrose 5% in water (D5W) or normal saline (sodium chloride solution 0.9%) per the Pharmacy Manual	See local prescribing information	See local prescribing information	See local prescribing information
Unit Dose Strength(s)	300 mg/20 mL	See local prescribing information	See local prescribing information	See local prescribing information
Dosage Level(s)	240 mg/m^2 administered on Days 1 and 8 of each 21-day chemotherapy cycle and on Day 1 of each 14-day maintenance cycle	1000 mg/m^2 administered on Days 1 and 8 of each 21-day chemotherapy cycle	Cisplatin eligible: cisplatin 70 mg/m^2 administered on Day 1 of each 21-day chemotherapy cycle (split dosing allowed as presented in Section 9.3.1.1) Cisplatin ineligible: The dose of carboplatin will be calculated using the Calvert formula with a target AUC = 4.5. on Day 1 of each 21-day chemotherapy cycle	800 mg administered on Day 1 of each 14-day maintenance cycle
Route of Administration	IV	IV	IV	IV
Infusion Time	30 minutes	Per Institution standards	Per Institution standards	60 minutes

AUC=area under the concentration-time curve; IV=intravenous; PD-L1=programmed death-ligand 1.
Other platinum-based chemotherapies, such as methotrexate/carboplatin/vinblastine (M-CAVI) for example, are not permitted in this study.

9.1.1. Dose, Dosing Regimen, and Route

Trilaciclib must be administered before gemcitabine, cisplatin/carboplatin and avelumab. Gemcitabine should be administered before cisplatin/carboplatin.

9.1.1.1. Trilaciclib

Trilaciclib for injection, 300 mg/vial (also referred to as "Trilaciclib Sterile Powder for concentrate for solution for IV infusion, 300 mg/vial") is supplied as a sterile, preservative-free, yellow, lyophilized cake in a single-dose vial (300 mg/20 mL).

Trilaciclib must be reconstituted and further diluted prior to IV infusion as outlined in the Pharmacy Manual. Aseptic technique must be used for reconstitution and dilution. Upon reconstitution, the solution must then be diluted to the calculated dose based on the body surface area (BSA) of the patient. Actual body weight should be utilized for dose calculations. If there is a change in body weight ≥10% relative to the weight at the time of the last dose calculation, dose should be recalculated. Recalculation of dose more frequently per local institutional guidelines is permitted. Dose recalculation to adjust for changes in body weight will not be considered a dose reduction and will be made at the discretion of the Investigator. No trilaciclib dose reductions for toxicity management will be allowed during the study.

9.1.1.1.1. Administration of Trilaciclib (For Arm B patients only)

- Administer diluted trilaciclib solution as a 30-minute IV infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered or within 4 hours prior to the start of avelumab on each day avelumab is administered. Do not administer trilaciclib as a bolus.
- Trilaciclib is always administered first. Results from hematology labs should be reviewed prior to administration of trilaciclib. If administration of platinum-based chemotherapy is skipped or discontinued, trilaciclib will also be skipped or discontinued.
- If administration of avelumab maintenance therapy is delayed or skipped, then trilaciclib should be administered as scheduled. If administration of avelumab maintenance therapy is permanently discontinued, trilaciclib will also be permanently discontinued.
- Diluted trilaciclib solution must be administered with an infusion set, including an in-line filter (0.2 or 0.22 micron). Compatible in-line filters include polyether sulfone, polyvinylidene fluoride, and cellulose acetate.
- Do not administer diluted trilaciclib solution with a polytetrafluorethylene (PTFE) in-line filter. PTFE in-line filters are not compatible with diluted trilaciclib solution.
- Do not co-administer other drugs through the same infusion line.
- Do not co-administer other drugs through a central access device unless the device supports co-administration of incompatible drugs.

If there is any study drug remaining in the infusion bag at the end of the 30 minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. Upon completion of infusion of diluted trilaciclib solution, the infusion line/cannula must be flushed with at least 20 mL sterile dextrose 5% in water (D5W) or 0.9% normal saline.

The infusion rate may be decreased to manage an infusion-related AE; for example, if a patient experiences a burning sensation during infusion, the duration of infusion may be increased to 45 minutes (or longer if clinically indicated) to alleviate the symptoms.

9.1.1.2. Gemcitabine and Cisplatin or Carboplatin

Descriptions of the formulations of commercially-available gemcitabine and cisplatin or carboplatin can be found in the respective current prescribing information/summary of product characteristics. Protocol-specified doses of gemcitabine and cisplatin or carboplatin will be administered IV in accordance with institutional guidelines and the recommended instructions below. Deviation from the recommendations provided in this protocol in order to follow institutional guidelines must receive prior approval from the Medical Monitor or Sponsor.

Patients will be eligible to receive 4-6 cycles of gemcitabine + carboplatin/cisplatin treatment, per Investigator's discretion. Other platinum-based chemotherapies, such as M-CAVI for example, are not permitted in this study.

Anti-emetic prophylaxis may be administered at the Investigator's discretion per institutional guidelines. To reduce effects on the immune system, the use of dexamethasone as an antiemetic should be minimized where possible; however, since this is a moderately emetogenic regimen, dexamethasone on the day of platinum-based chemotherapy is allowed per the American Society of Clinical Oncology (ASCO) guidelines (Hesketh, 2017).

Patients treated with cisplatin should receive pre-treatment hydration per institutional guidelines. Maintain adequate hydration and urinary output for 24 hours after cisplatin administration.

Patients will be allowed to switch from cisplatin to carboplatin chemotherapy if they become ineligible for cisplatin due to toxicity, or from carboplatin to cisplatin chemotherapy in the event that patient becomes eligible to receive cisplatin. Changes in protocol chemotherapy will not be allowed for the reason of suspected or confirmed disease progression by RECIST v1.1.

Ineligibility to receive cisplatin-based chemotherapy should be based upon the criteria published by Galsky et al. (Galsky, 2011) and will be documented in the eCRF. Patients who meet at least one of the following criteria should be considered for treatment with carboplatin plus gemcitabine; however, the final decision will be made by the Investigator:

- Impaired renal function (GFR >30 but <60 mL/min)
- NCI-CTCAE v5.0 Grade ≥2 audiometric hearing loss of 25 decibels at two contiguous frequencies
- NCI-CTCAE v5.0 Grade ≥2 peripheral neuropathy (i.e., sensory alteration or paresthesia, including tingling)

Needles or IV administration sets containing aluminum parts that may come in contact with cisplatin or carboplatin should not be used for the preparation or administration of the drug.

Aluminum can react with cisplatin or carboplatin causing precipitate formation and loss of potency.

Trilaciclib is always administered first, followed by gemcitabine + carboplatin/cisplatin which may be administered immediately following trilaciclib, but not until the completion of the trilaciclib infusion. The interval between trilaciclib administration and the first dose of gemcitabine + carboplatin/cisplatin administration should not be greater than 4 hours. If gemcitabine + carboplatin/cisplatin therapy is discontinued or skipped, trilaciclib will also be discontinued or skipped.

9.1.1.2.1. Dose Calculation Recommendations

Patients who have a ≥10% weight change relative to the weight at the time of the last dose calculation, or as per institutional standards, will require recalculation of the dose for subsequent cycles. Dose recalculation to adjust for changes in body weight will not be considered a dose reduction and will be made at the discretion of the Investigator.

For patients who are cisplatin ineligible, the carboplatin dose should be calculated using Calvert formula with a target AUC = 4.5 administered IV on Day 1 of each 21-day cycle.

In patients who require carboplatin dose modification, if creatinine at the time of the dose modification is lower than the baseline creatinine that was used, the prior (higher) creatinine value should be used. This is to ensure that patients receive the intended dose reduction. In patients with abnormally low serum creatinine, a minimum of 0.7 mg/dL should be used for the calculation of dose. The maximum carboplatin dose based on target AUC will be capped at 675 mg.

9.1.1.3. Avelumab

A description of the formulation of commercially-available avelumab can be found in the local prescribing information/summary of product characteristics. Avelumab will be administered IV in accordance with institutional guidelines and the recommended instructions below. Deviation from the recommendations provided in this protocol in order to follow institutional guidelines must receive prior approval from the Medical Monitor.

Avelumab 800 mg will be administered IV on Day 1 of each 14-day maintenance cycle as a 60-minute infusion. In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory for the first 4 infusions (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity or prior infusion reactions.

Sites should make every effort to target infusion timing to be as close to 60 minutes as possible. However, given the variability of infusion pumps from site to site, time windows of -10 minutes and +20 minutes is permitted (i.e., infusion time is 60 minutes -10 min/+20 min). Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 9.3.3.

No dose reductions for toxicity management will be allowed during the study.

Trilaciclib is always administered first, followed by avelumab which may be administered immediately following trilaciclib, but not until the completion of the trilaciclib infusion. The interval between the completion of trilaciclib administration and avelumab administration should not be greater than 4 hours. If avelumab therapy is delayed or skipped, trilaciclib should be administered as scheduled. If avelumab therapy is permanently discontinued, trilaciclib should also be permanently discontinued.

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Patients without progressive disease as per RECIST v1.1 guidelines (i.e., with an ongoing CR, PR, or SD) following completion of 4-6 cycles of platinum-based chemotherapy may receive avelumab in maintenance until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of avelumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of avelumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- Prothrombin time, partial thromboplastin time, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- Lactate dehydrogenase
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Other immune-related AEs attributed to avelumab not listed above should be assessed by the Investigator and discussed with the medical monitor to determine if avelumab should be held or discontinued.

If corticosteroids have been initiated as part of the immune-related AE management, avelumab can be resumed with complete or partial resolution (Grade 0 or 1) of the AE after corticosteroid taper – refer to the local prescribing information/summary of product characteristics (Bavencio, 2020 [US]; Bavencio, 2020 [EU]).

9.1.2. Preparation, Handling, Storage, and Accountability

The Investigator or institution is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The

Investigator/institution may assign some or all of the Investigator's/institution's duties for investigational product(s) accountability to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator/institution.

Further guidance and information are provided in the Pharmacy Manual.

9.1.3. Treatment Compliance

The Investigator or Designee will dispense the study drug, via a Pharmacist/Designee, only for use by patients enrolled in the study as described in this protocol (Section 9.7). The study drug is not to be used for reasons other than those described in this protocol. The clinical study site will maintain records of study drug receipt, preparation, and dispensing, including the applicable lot and vial numbers; patient's height, body weight, and BSA; date and time of the start and end of each trilaciclib, avelumab, gemcitabine, and cisplatin or carboplatin infusion; and total drug administered in milligrams.

9.2. Criteria for Starting Cycle 1 and Each Subsequent Chemotherapy Cycle

Patients must meet specific hematologic criteria for each platinum-based chemotherapy dosing day and any non-hematologic toxicities (except alopecia) must be ≤Grade 2 or have returned to baseline. Please note the ANC for Cycle 1 Day 1 is required to be ≥1.5 x 10^9/L (Table 7).

For dose delays due to toxicity, the patient should be followed (at least) weekly to monitor the toxicity until treatment criteria are met or until they discontinue treatment. If the Day 1 or Day 8 doses are delayed, any assessments completed as part of the planned Day 1 visit will be captured in the eCRF as unscheduled visits.

Patients enrolled in the study will be eligible to receive 4-6 cycles of platinum-based chemotherapy, per Investigator's discretion.

9.3. Toxicity Management and Dose Modifications

The dose of trilaciclib will not be modified and will remain at 240 mg/m^2 throughout the study. Trilaciclib is always administered first. If administration of gemcitabine + carboplatin/cisplatin chemotherapy is discontinued, trilaciclib will also be discontinued. If administration of avelumab maintenance therapy is discontinued, trilaciclib will also be discontinued. If administration of chemotherapy is delayed or skipped, trilaciclib will also be delayed or skipped. If administration of avelumab is delayed or skipped, then trilaciclib should be administered as scheduled.

Gemcitabine and carboplatin/cisplatin dose reductions are permitted according to the organ system showing the greatest degree of drug-related toxicity per Investigator discretion and institutional guidelines; recommendations are provided in Table 7, Table 8, and Section 9.3.1.1. Toxicities will be graded according to the NCI-CTCAE, Version 5.0.

No dose reductions will be allowed for avelumab during the study.

Management of AEs may include decreasing the infusion rate (that is, extending the infusion time) for avelumab, administration of corticosteroids, delay of a scheduled dose, or discontinuation of therapy. The total infusion time for avelumab should not exceed 120 minutes. Refer to the current avelumab prescribing information/summary of product characteristics for

guidance on the management of avelumab-related AEs (Bavencio, 2020 [US]; Bavencio, 2020 [EU]).

9.3.1. Dose Modifications for Hematologic and Non-Hematologic Toxicity during Chemotherapy Period

Gemcitabine + carboplatin/cisplatin dose reductions for hematologic toxicities are based on values obtained within 24 hours of chemotherapy on Day 1 or Day 8 of a cycle per Investigator discretion and institutional guidelines; recommendations are provided in Table 7, Table 8, and Section 9.3.1.1). Gemcitabine + carboplatin/cisplatin dose modifications for non-hematologic toxicities may occur at any time during chemotherapy treatment per Investigator discretion and institutional guidelines; recommendations are provided in Table 7, Table 8, and Section 9.3.1.1. Secondary prophylactic G-CSF is strongly recommended to avoid the need for dose reductions for neutropenia; however, primary prophylactic G-CSF use during Cycle 1 (i.e., prior to the actual Cycle 2 Day 1 dosing visit) is not allowed.

Table 7: Recommended Dose Modification for Hematologic Toxicity during Chemotherapy Period

Lab Value	Time point	Gemcitabine + Carboplatin or Cisplatin and G-CSF [b] Recommendations	Trilaciclib
ANC ≥1.0 x 10^9/L[a] **AND** platelets ≥100 x 10^9/L	Day 1 or 8 of any cycle	No dose reduction	Trilaciclib is given only on days that chemotherapy is given. If both chemotherapy drugs are held, trilaciclib is held. No dose reductions are permitted for trilaciclib.
ANC <1.0 x 10^9/L **OR** platelets <100 x 10^9/L	Day 1 of any cycle	**Hold chemotherapy.** Recheck CBC weekly. Once ANC ≥1.0 x 10^9/L AND platelets ≥100 x 10^9/L, restart drugs depending on toxicity: If chemotherapy was held for ANC <1.0 x 10^9/L, restart drugs at the same dose and add G-CSF [b] with each subsequent cycle. If Day 1 is held for neutropenia in the setting of G-CSF [b] use, then administer drugs at next lower dose (see Section 9.3.1.1) and continue G-CSF [b] with each subsequent cycle. If chemotherapy was held for platelets <100 X 10^9/L, administer drugs at next lower dose (see Section 9.3.1.1).	
ANC ≥0.75 x 10^9/L but <1.0 x 10^9/L **OR** platelets ≥75 x 10^9/L but <100 x 10^9/L	Day 8 of any cycle	If ANC <1.0 x 10^9/L and no prior use of G-CSF [b], then administer both drugs at the same dose and add G-CSF with this cycle and subsequent cycles. If ANC <1.0 x 10^9/L in the setting of G-CSF [b] use, then administer drugs at next lower dose and continue G-CSF [b] in this cycle and subsequent cycles. If platelets <100 x 10^9/L, then administer drugs at next lower dose.	
ANC <0.75 x 10^9/L **OR** platelets <75 x 10^9/L	Day 8 of any cycle	**Hold chemotherapy.** Recheck CBC weekly. Once ANC ≥1.0 x 10^9/L AND platelets ≥100 x 10^9/L (Day 1 criteria are met), restart drugs at next lower dose (see Section 9.3.1.1), which will be considered Day 1 of the next cycle and Day 8 will not be made up. If chemotherapy was held for ANC <0.75 x 10^9/L, administer G-CSF [b] with each subsequent cycle.	
Febrile neutropenia **OR** platelet <50 x 10^9/L with bleeding	At any time	**Hold chemotherapy.** Recheck CBC weekly. Once ANC ≥1.0 x 10^9/L AND platelets ≥100 x 10^9/L, restart drugs at next lower dose (see Section 9.3.1.1), which will be considered Day 1 of the next cycle and Day 8 will not be made up if it had not yet occurred. For febrile neutropenia, administer G-CSF [b] with subsequent cycles.	

ANC=absolute neutrophil count; CBC=complete blood count; G-CSF=granulocyte colony-stimulating factor; RBC=red blood cell

[a] Except for Cycle 1 Day 1 where ANC is required to be ≥1.5 x 10^9/L.

[b] Use of prophylactic colony stimulating factors (e.g., G-CSF; granulocyte-macrophage colony-stimulating factor) during Cycle 1 (i.e., prior to the actual Cycle 2 Day 1 dosing visit) is not allowed.

Table 8: Recommended Dose Modifications for Non-Hematologic Toxicity during Chemotherapy Period

NCI-CTCAE Grade	Action Taken	
	Gemcitabine + Carboplatin or Cisplatin	**Trilaciclib [a]**
Grade 1-2	No change in dose	Trilaciclib is given only on days that chemotherapy is given. If both chemotherapy drugs are held, trilaciclib is held. No dose reductions are permitted for trilaciclib.
≥Grade 3	Hold both drugs. Once toxicity resolves to ≤Grade 2 or baseline, restart gemcitabine at the next lower dose and carboplatin or cisplatin at the same dose (or at next lower dose per discretion of Investigator) (Section 9.3.1.1).	

NCI-CTCAE=National Cancer Institute–Common Terminology Criteria for Adverse Events v5.0
[a] Arm B only.

9.3.1.1. Recommended Dose Reductions of Gemcitabine and Cisplatin or Carboplatin for Hematologic and Non-Hematologic Toxicity

For hematologic toxicity requiring a dose reduction, chemotherapy drug doses will be reduced based on institutional guidelines. If a patient experiences any toxicity requiring a third dose reduction, either gemcitabine or carboplatin/cisplatin will be discontinued (at discretion of the Investigator) and the other chemotherapy drug (with or without trilaciclib) may be continued. If a patient experiences additional toxicity requiring further dose reductions, all study drugs will be permanently discontinued.

All dose reductions are permanent and no dose increases will occur following a dose reduction.

The recommended dose reductions for **gemcitabine** following a hematologic or non-hematologic toxicity are as follows:

- Starting dose: 1000 mg/m^2
- First dose reduction: 800 mg/m^2
- Second dose reduction: 600 mg/m^2
- Third dose reduction: continue only one chemotherapy
- Fourth dose reduction: discontinue all study drugs

The recommended dose reductions for **carboplatin** following a hematologic or non-hematologic toxicity are as follows:

- Starting dose: AUC=4.5
- First dose reduction: 20% from original dose
- Second dose reduction: 40% from original dose
- Third dose reduction: continue only one chemotherapy
- Fourth dose reduction: discontinue all study drugs

The recommended dose reductions for **cisplatin** following a hematologic or non-hematologic toxicity are as follows:

- Starting dose: 70 mg/m^2
- First dose reduction: 60 mg/m^2 (splitting the dose of cisplatin to Day 1 and Day 8 dosing is an allowed alternative)
- Second dose reduction: 50 mg/m^2 (splitting the dose of cisplatin to Day 1 and Day 8 dosing is an allowed alternative)
- Third dose reduction: continue only one chemotherapy
- Fourth dose reduction: discontinue all study drugs

9.3.2. Recommended Actions with Trilaciclib for Adverse Events of Special Interest

Recommended actions to be taken with trilaciclib following an AESI are provided in Table 9.

Table 9: Recommended Actions with Trilaciclib Following Adverse Events of Special Interest

AESI	Severity (NCI-CTCAE)	Recommended Action
Injection-site reactions including phlebitis and thrombophlebitis	Grade 1: Tenderness with or without symptoms (e.g., warmth, erythema, itching)	Interrupt or slow infusion of trilaciclib. If 0.9% Sodium Chloride Injection, USP, is being used as a diluent/flush, consider changing to 5% Dextrose Injection, USP as appropriate for subsequent infusions.
	Grade 2: Pain; lipodystrophy; edema; phlebitis	Interrupt infusion of trilaciclib. If pain not severe, follow instructions for Grade 1. Otherwise, stop infusion in extremity and rotate site of infusion to site in alternative extremity. If 0.9% Sodium Chloride Injection, USP is being used as a diluent/flush, consider changing to 5% Dextrose Injection, USP as appropriate for subsequent infusions. Central access may also be considered.
	Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated. Grade 4: Life-threatening consequences; urgent interventions indicated.	Stop infusion and permanently discontinue trilaciclib.

AESI	Severity (NCI-CTCAE)	Recommended Action
Acute drug hypersensitivity reactions	Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)	Stop infusion and hold trilaciclib until recovery to Grade ≤1 or baseline, then consider resuming trilaciclib. If Grade 2 recurs, permanently discontinue trilaciclib.
	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. OR Grade 4: Life-threatening consequences; urgent intervention indicated.	Permanently discontinue trilaciclib.
ILD/pneumonitis	Grade 2 (symptomatic)	Hold trilaciclib until recovery to Grade ≤1 or baseline, then consider resuming trilaciclib. If Grade 2 recurs, permanently discontinue trilaciclib.
	Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated. OR Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue trilaciclib.
Other toxicities	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Hold trilaciclib until recovery to Grade ≤1 or baseline, then consider resuming trilaciclib. If Grade 3 recurs, permanently discontinue trilaciclib.
	Grade 4: Life-threatening consequences; urgent intervention indicated.	Permanently discontinue trilaciclib.

AESI=adverse event of special interest; ILD=interstitial lung disease; NCI-CTCAE=National Cancer Institute–Common Terminology Criteria for Adverse Events; USP=United States Pharmacopeia.

9.3.3. Recommended Actions with Avelumab for AESIs

Any AE that is suspected to be a potential immune-related AE (irAE) is considered an avelumab AESI.

See Section 9.1.1.3 for further details on associated risks of treatment with avelumab.

The recommended actions for the management of irAEs are provided in Table 10 and Table 11 below. Refer to the current avelumab prescribing information/summary of product characteristics for additional guidance on the management of avelumab AESIs (Bavencio, 2020 [US]; Bavencio, 2020 [EU]).

As with all monoclonal antibody therapies, avelumab can induce flu-like symptoms. For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable nonsteroidal anti-inflammatory drug dose (e.g., ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at Investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (e.g., paracetamol or ibuprofen) and rigors (e.g., meperidine) may be given to patients at the discretion of the Investigator.

Table 10: Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Temporarily decrease avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the patient. Patients have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on Investigator's medical judgment. The total infusion time for avelumab should not exceed 120 minutes. - If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice.	

IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NSAID=nonsteroidal anti-inflammatory drug.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions: In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 10 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H2-blocker

antihistamines (e.g., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

Table 11: Management of Avelumab Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: treat as Grade 2, 3 or 4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤1: resume avelumab therapy If persists >5-7 days or recurs: treat as Grade 3 or 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3) If worsens, persists >3 to 5 days, or recurs after improvement: add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis

Dermatological irAEs		
Grade of Rash (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If Grade 2 persists >1 to 2 weeks or recurs: withhold avelumab therapy; consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper If worsens: treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area Grade 4: Life threatening consequences	Withhold avelumab for Grade 3 Permanently discontinue for Grade 4 or recurrent Grade 3 Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3)
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: treat as Grade 2 or Grade 3 to 4

Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: when symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurring Grade 2: treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia Grade 4: Life-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: taper steroids over at least 1 month If not improving after 48 hours or worsening: add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT >ULN to 3.0 × ULN and/or Total bilirubin >ULN to 1.5 × ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤5 x ULN and/or total bilirubin > 1.5 to ≤3 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: resume routine monitoring; resume avelumab therapy If elevation persists >5 to 7 days or worsens: treat as Grade 3 to 4

Grade 3 to 4 AST or ALT >5 × ULN and/or total bilirubin >3 × ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤1: taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: add mycophenolate mofetil 1 g twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased >ULN to 1.5 × ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: treat as Grade 2 to 3 or 4
Grade 2 to 3 Creatinine increased >1.5 and ≤6 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: taper steroids over at least 1 month, and resume avelumab therapy following steroids taper If worsens: treat as Grade 4
Grade 4 Creatinine increased >6 × ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: taper steroids over at least 1 month

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g., troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	Withhold avelumab therapy Hospitalize In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management Cardiology consult to establish etiology and rule-out immune-mediated myocarditis Guideline-based supportive treatment as per cardiology consult* Consider myocardial biopsy if recommended per cardiology consult	If symptoms improve and immune mediated etiology is ruled out, re-start avelumab therapy If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis
Immune-mediated myocarditis	Permanently discontinue avelumab Guideline-based supportive treatment as appropriate as per cardiology consult* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A)
*Local guidelines, or e.g., ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate Rule-out secondary endocrinopathies (i.e., hypopituitarism/hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate Rule-out secondary endocrinopathies (i.e., hypopituitarism/hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression) Continue hormone replacement/suppression and monitoring of endocrine function as appropriate

Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e., subnormal serum free T4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement) In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented Continue hormone replacement/suppression therapy as appropriate
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE

Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: taper steroids over at least 1 month and resume avelumab therapy following steroids taper
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: taper steroids over at least 1 month
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult	If improves to Grade ≤1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT=computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin; T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

Table 12: Recommended Treatment Modification for Other Avelumab Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification
Drug-related adverse reactions (excluding infusion-related reaction / hypersensitivity and immune-related AE)	Grade 1	Continue avelumab therapy
	Grade 2	Continue avelumab therapy
	Grade 3	Withold avelumab until recovery to Grade ≤1 or baseline If toxicities do not resolve to Grade ≤1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs, permanently discontinue avelumab Exceptions are: Laboratory values out of normal range that do not have any clinical correlate
	Grade 4	Permanently discontinue avelumab Exceptions are: Laboratory values out of normal range that do not have any clinical correlate

9.3.4. Hy's Law Management

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

Patients who present with the following laboratory abnormalities should be evaluated further to determine the etiology of the abnormal laboratory values:

- Baseline AST or ALT and total bilirubin values are within the normal range and the patient subsequently presents with AST or ALT ≥3 × ULN concurrent with a total bilirubin ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 × ULN or not available.
- Pre-existing baseline ALT, AST, OR total bilirubin values are above the ULN, and the patient subsequently presents with:
  - AST or ALT ≥2 × baseline value AND ≥3 × ULN, or ≥8 × ULN (whichever is smaller)
  - **concurrent** with total bilirubin ≥2 × baseline value OR ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events (SAEs).

9.3.5. Management of Nausea and Vomiting

Necessary supportive care (e.g., antiemetics, antidiarrheals) administered per the standard of care at the study center will be permitted. See Section 9.4 for guidance on the use of growth factors (colony-stimulating factors and ESAs) during the study. To reduce effects on the immune system, the use of dexamethasone as an antiemetic should be minimized where possible; however, since this is a moderately emetogenic regimen, dexamethasone on the day of gemcitabine + carboplatin/cisplatin is allowed per the ASCO guidelines (Hesketh, 2017).

9.4. Supportive Care Interventions

9.4.1. Colony Stimulating Factor Usage

Use of primary prophylactic colony-stimulating factors (e.g., G-CSF; granulocyte-macrophage colony-stimulating factor [GM-CSF]) during Cycle 1 (i.e., prior to the actual Cycle 2 Day 1 dosing visit) is not allowed. In subsequent cycles (Cycle 2 and beyond), prophylactic colony-stimulating factors are allowed as outlined in Table 7, which are based on the ASCO guidelines for neutropenia (Smith, 2015) and package inserts/summary of product characteristics. If in any cycle (including Cycle 1), a patient experiences febrile neutropenia and is at high risk for infection-associated complications, G-CSF/GM-CSF may be used to treat the febrile neutropenia event per ASCO guidelines and package inserts/summary of product characteristics. If a patient has risk factors that are predictive of poor clinical outcomes (Table 12), G-CSF/GM-CSF may also be used as prophylaxis, except during Cycle 1.

Short acting G-CSF products (i.e., Neupogen or biosimilars) may be administered starting 24 to 48 hours after the dose of chemotherapy on Day 1 or Day 8 and must be stopped 48 hours prior to the next chemotherapy administration. Due to its prolonged half-life, pegfilgrastim may only be used if the patient received Day 8 chemotherapy; it should be administered 24 to 48 hours after the dose of Day 8 chemotherapy.

Table 13: Patient Risk Factors for Poor Clinical Outcomes Resulting from Febrile Neutropenia or Infection

Risk Factor
Sepsis syndrome
Age > 65 years
Profound neutropenia (absolute neutrophil count <0.1 × 10^9/L)
Neutropenia expected to last > 10 days
Pneumonia
Invasive fungal infection
Other clinically documented infections
Hospitalization at time of fever
Prior episode of febrile neutropenia

ASCO=American Society of Clinical Oncology
Source: Table recreated from Table 2 of the ASCO guidelines (Smith, 2015; Smith, 2006).

9.4.2. Erythropoiesis-Stimulating Agent Usage

If a patient experiences a hemoglobin level <10.0 g/dL or symptomatic anemia after receiving the first dose of study treatment, ESAs may be used per the current prescribing information (Bohlius, 2019) (Procrit®, 2017; Aranesp®, 2011).

9.4.3. Transfusions

Red Blood Cells

Based on the NCCN Clinical Practice Guidelines in Oncology for Hematopoietic Growth Factors Version 2.2020 and the AABB Clinical Practice Guidelines, the following RBC transfusion thresholds are recommended (Carson, 2016; Goel, 2017); however, the patient's clinical situation should always be the primary guiding factor when deciding to transfuse.

- Transfusion is not indicated until the hemoglobin level is ≤7 g/dL for hospitalized adult patients who are hemodynamically stable.
- An RBC transfusion threshold of ≤8 g/dL is recommended for patients undergoing orthopedic surgery, cardiac surgery, and those with preexisting cardiovascular disease.
- Patients with symptomatic anemia should be transfused per the Investigator discretion regardless of hemoglobin levels.

Platelets

Platelet transfusion is recommended at a threshold of ≤10 x 10^9/L. Platelets should also be transfused in any patient who is bleeding with a platelet count <50 x 10^9/L (100 x 10^9/L for central nervous system or ocular bleeding) (Kaufman, 2015; Schiffer, 2017).

9.5. Prior/Concomitant Medications and Procedures

All concomitant medications including prescription medications, over-the-counter preparations, growth factors, and blood products from informed consent through 90 days after the last dose of study treatment (90-day Safety Follow-up Visit) will be documented, where possible.

Any diagnostic, therapeutic, or surgical procedures performed during the study period will be documented. Documentation will include information regarding the date(s), indication(s), description of the procedure(s), and any clinical or pathological findings, if available.

9.5.1. Concomitant Surgery

In the case that a surgical procedure is required for palliative care, all attempts should be made to rule out disease progression beforehand.

In the case of a surgical procedure, study treatment should be withheld. Postoperatively, the decision to reinitiate study treatment should be discussed with the Medical Monitor.

9.5.2. Concomitant Radiotherapy

Local radiotherapy of isolated lesions with palliative intent is acceptable (e.g., bleeding, pain, compression), however all attempts should be made to rule out disease progression.

Palliative radiotherapy is permitted if considered medically necessary by the treating physician. If palliative radiotherapy is needed to control pain, the site(s) of disease-causing pain should also be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered a sign of disease progression.

9.6. Prohibited Therapy

Administration of other concomitant non-protocol anticancer or herbal therapies prior to disease progression is not permitted while on this study. This includes any low-dose systemic chemotherapeutic agent given for a non-oncologic purpose (e.g., low-dose methotrexate for rheumatoid arthritis). Palliative radiotherapy/surgery is allowed to control disease symptoms, but not to aid in the response of the tumor. If palliative radiotherapy/surgery includes a lesion being followed by RECIST in this study, that lesion must be identified accordingly in the eCRF. Administration of other concomitant investigational agents for any indication is not permitted while on this study.

Patients who have achieved a PR or CR of target lesions and who develop new lesions (≤3 lesions) that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per the Investigator.

9.6.1. Trilaciclib

Avoid concomitant use of trilaciclib with certain OCT2, MATE1, and MATE2-K substrates (e.g., dofetilide, dalfampridine) where minimal concentration changes may lead to serious or life-threatening toxicities. Refer to the prescribing information for these concomitant medications for assessing the benefit and risk of concomitant use of trilaciclib (Section 4.5.2.2).

9.6.2. Gemcitabine

Gemcitabine is not indicated for use in combination with radiation therapy. Patients should not receive gemcitabine within 7 days before or after radiation therapy. Concurrent therapy (given together or ≤7 days apart) with gemcitabine and thoracic radiation has led to life-threatening

mucositis, especially esophagitis and pneumonitis. Excessive toxicity has not been observed when gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive gemcitabine after prior radiation.

9.6.3. Carboplatin

Although carboplatin has limited nephrotoxic potential, caution should be exercised when administering carboplatin with aminoglycosides, which has resulted in increased renal and/or audiologic toxicity. Any medication that is contraindicated when using gemcitabine or carboplatin is not permitted, and special warnings and precautions for use of gemcitabine or carboplatin should be observed.

Caution should be exercised with concomitant use of drugs that are substrates for OCT2 with narrow therapeutic index (Section 4.5.1.2).

9.6.4. Cisplatin

Simultaneous use of myelosuppressive agents or radiation will boost the effects of cisplatin's myelosuppressive activity. The occurrence of nephrotoxicity caused by cisplatin may be intensified by concomitant treatment with antihypertensive agents containing furosemide, hydralazine, diazoxide, and propranolol.

Concomitant administration of ototoxic (e.g., aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function.

Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes, or trimethobenzamides may mask ototoxic symptoms (such as dizziness and tinnitus).

In the event of the simultaneous use of oral anticoagulants, it is advisable to more frequently check the INR.

9.6.5. Avelumab

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the avelumab maintenance period. These agents, in combination with avelumab, could potentially increase the risk for autoimmune conditions. Patients are also not allowed to receive live attenuated vaccines during the avelumab maintenance period.

Patients should not receive bisphosphonate or denosumab treatment unless it has been initiated more than 14 days prior to receiving the first dose of avelumab.

Avelumab should not be given to patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications (including but not limited to cyclophosphamide, sirolimus, tacrolimus, azathioprine, methotrexate, thalidomide, and anti- tumor necrosis factor agents) within 14 days of avelumab administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

Clarifications About Steroid Use: Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes (Khan, 2008; Schleimer, 1984). Furthermore, as with all immunotherapies intended to augment T cell-mediated immunity, there

is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 agents indicate that short-term use of steroids may be employed without compromising clinical outcomes (Weber, 2010). Therefore, the use of steroids during avelumab maintenance is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of immune-related AEs, steroids are permitted according to institutional guidelines.
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- Prophylactic use, e.g., for the prevention of acute infusion-related reactions, is prohibited, ***except*** prophylactic use prior to CT or MRI.

The above lists of medications are not necessarily comprehensive. The Investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

9.7. Measures to Minimize Bias: Randomization and Blinding

The study will be randomized and open-label.

Patients meeting all inclusion and exclusion criteria will be stratified according to the stratification factors of presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin). Patients will be randomly assigned in a 1:1 ratio to platinum-based chemotherapy followed by avelumab maintenance therapy (Arm A) or trilaciclib + platinum-based chemotherapy followed by trilaciclib + avelumab maintenance therapy (Arm B) by an interactive web response system (IWRS) according to a randomization schedule generated by an external statistician. A patient who is randomized and discontinues from the study, even if no study drug was administered, will not be replaced.

If a patient does not receive the correct study treatment for their allocated treatment arm, the reason must be clearly documented in eCRF. The patient will remain on study and continue to receive the same study treatment, all data will be collected, and follow-up will continue as described in Schedule of Assessments table (Table 5).

Details regarding the preparation and administration of trilaciclib, platinum-based chemotherapy, and avelumab will be included in the Pharmacy Manual.

9.8. Intervention after End of Study Treatment

Following completion of study treatment on the study, patients will receive treatment as determined by their healthcare provider. During Survival Follow-up, the patient (or legally authorized representative where allowed by local regulation) will be contacted to record their status (alive or dead) as well as details of any subsequent systemic anti-cancer therapy initiated (see Section 11.8).

10. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

10.1. Discontinuation of Study Treatment

Study drugs will be discontinued if any of the following events occur during the study:

- A patient suffers an AE that, in the judgment of the Investigator, Sponsor, or Medical Monitor, presents an unacceptable risk to the patient
- General or specific changes in the patient's condition (e.g., a significant intercurrent illness or complication) that, in the judgment of the Investigator, are unacceptable for further administration of study drug
- Occurrence of pregnancy in a female patient during the study
- Significant noncompliance with protocol requirements
- The Sponsor or legal representative of the Sponsor requests the patient to withdraw
- Patient has documented disease progression (radiographic or clinical progression). Local treatment of isolated lesion(s) with palliative radiation therapy or surgery is permitted to control disease symptoms but not to aid in the response of the tumor (see Section 9.5). Patients requiring palliative radiation may continue receiving study drug until documented disease progression (radiographic or clinical) if, in the Investigator's opinion, the patient is continuing to receive clinical benefit and they meet the requirements described in Section 11.2.1.1.
- If total time between chemotherapy exceeds a total of >42 days, unless agreed to by the treating Investigator and Medical Monitor.
- If total time between avelumab maintenance therapy exceeds a total >56 days, unless agreed to by the treating Investigator and Medical Monitor.
- Where permanent discontinuation of all study drugs is indicated in the toxicity management recommendations (Section 9.3).

At the time of study drug discontinuation, an End of Treatment Visit should be completed with assessments performed as shown in the Schedule of Assessments (Table 5). The Investigator or Designee will document the reason for study drug discontinuation on the applicable eCRF. When discontinuation is due to an SAE or a Grade 3 or 4 toxicity considered to be related to study drug, the Investigator should follow the event until resolution, return to baseline, or it is deemed that further recovery is unlikely. Data on these events should be collected on the AE eCRF. In the event a patient discontinues due to pregnancy, the Investigator or designee should notify the Medical Monitor by telephone within 24 hours of pregnancy confirmation (see Section 17.3).

10.2. Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. At the time of discontinuing from the study, if the patient has not already

discontinued study intervention, an End of Treatment Visit should be completed with assessments performed as shown in the Schedule of Assessments (Table 5).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator or designee must document this in the site study records.

If a patient withdraws consent for further study procedures, the site should clarify if the patient (or legally authorized representative where allowed by local regulation) remains open to survival contact and associated data collection. Public records may be used to verify survival status if permitted by institutional or country guidelines.

For those patients who have not progressed clinically or radiologically at the time of study drug discontinuation, every effort should be made to continue radiological tumor assessments, utilizing the same imaging modality as used at Screening as outlined in the Schedule of Assessments (Table 5), until progressive disease, initiation of subsequent anti-cancer therapy, withdrawal of consent, or study completion, whichever occurs first. Results of these scans should be assessed by RECIST 1.1 and data entered in electronic data capture (EDC) in the corresponding tumor assessment forms.

10.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

In general, a patient is considered lost to follow-up after there are at least 3 documented attempts to contact the patient. It is recommended that 1 attempt is via certified letter to the patient.

10.4. Study and Site Start and Closure

The overall study begins when the first patient signs the ICF. The overall study ends when the last patient completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the patient is unable to be contacted by the Investigator).

A study site is considered eligible to start participation in the study once all regulatory approvals are in place, site agreement contract is fully executed, and any other required documents are in place as required by Sponsor. The study ends when 60% of the randomized patients have died, which is estimated to be approximately 34 months after first patient is randomized.

The Sponsor reserves the right to close a study site(s) or terminate the study at any time for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, a study-site closure visit has been performed, and the site has closed all regulatory activities with the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The Investigator may be requested to initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Should this occur with patients receiving study drug, the patients will transition to receive standard of care treatment by their healthcare provider outside of this study.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further development of trilaciclib

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

11. STUDY ASSESSMENTS

Study procedures and their timing are summarized in the Schedule of Assessments (Table 5). Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Immediate safety concerns should be discussed with the study Medical Monitor upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

The Investigator or Designee will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., hematology, serum chemistry) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and are performed within the permitted 30-day Screening period.

11.1. Screening Assessments

The following information for screening failures should be recorded into appropriate eCRFs: patient ID, demographic data, and reason for failing the screening process. Patients may only be rescreened one time at the discretion of the Investigator. For abnormal laboratory values, a second test to confirm the first is permitted; only the qualifying result should be entered in the eCRF.

11.1.1. Documentation of Locally Advanced or Metastatic Urothelial Carcinoma

Eligibility will be based on locally advanced or metastatic urothelial carcinoma status from the most recent tumor biopsy report obtained prior to Screening.

Locally advanced or metastatic urothelial carcinoma status should be histologically confirmed by local pathology immunohistochemistry (IHC) assessment (see Inclusion Criterion 2).

11.1.2. Randomization

Eligibility will be determined prior to randomization and the start of study treatment. All eligible patients will be randomly allocated according to the randomization schedule and will receive a unique randomization number. Once a randomization number is assigned to patient, it can never be re-assigned to another patient.

Eligible patients will be instructed on all protocol requirements, including any restrictions on concomitant medication usage.

Randomization will be performed via IWRS following confirmation that the patient is eligible for the study.

11.1.3. Demographics

Age, gender, race (when reporting is allowed per local regulations), and ethnicity will be collected during the Screening Period.

11.1.4. Medical History and Urothelial Carcinoma Disease History

Medical and surgical history, including past and current conditions, will be collected. Concomitant medications taken within 30 days prior to the first dose of study drug through the End of Treatment Visit will be recorded.

Documentation of urothelial carcinoma history, including date of diagnosis, will be collected.

Prior radiation, surgery, and systemic chemotherapy for urothelial carcinoma will also be recorded.

11.2. Efficacy Assessments

11.2.1. Anti-tumor Efficacy Assessment

All sites of measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessment will be performed at the timepoints relative to Cycle 1 Day 1, as specified in the Schedule of Assessments (Table 5), regardless of drug (cycle) delays, skips, or interruptions. Tumor assessments will continue until disease progression, withdrawal of consent, initiation of subsequent anti-cancer therapy, or study completion, whichever occurs first.

Baseline imaging should include CT (preferred) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Brain scan (MRI preferred) during screening is not required and should be performed per investigator discretion based on clinical signs and symptoms. Bone scan or Positron Emission Tomography (PET) (such as [^{18}F]-fluorodeoxyglucose [FDG]-PET, sodium fluoride [NaF]-PET, or other locally available PET options) should also be performed in all patients to evaluate for bone metastases at baseline. Bone lesion(s) identified at baseline by bone scan will be further assessed by CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by CT or MRI as per the tumor assessment schedule as an alternative to bone scans. If bone metastases cannot be seen on CT or MRI scans, bone scans, or PET should be repeated, using the same diagnostic procedure bone metastases were at baseline, when CR is identified in target disease or when progression in bone is suspected. Any CT, MRI, bone scan, or PET obtained as standard of care prior to screening visit will not need to be repeated as long as those imaging tests were obtained within 30 days prior to the date of randomization.

After baseline tumor assessments, evaluation of tumor response per RECIST v1.1 will be performed every 6 weeks (±7 days) during the chemotherapy period and every 8 weeks (±7 days) during the avelumab maintenance period for up to 1 year relative to Cycle 1 Day 1 and every 12 weeks (±7 days) thereafter relative to Cycle 1 Day 1, until documented disease progression or subsequent anticancer therapy; additional scans may be performed as clinically indicated. Bone scans will only be repeated during the study as clinically indicated or considered local standard of care (e.g., patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) and at the time of CR confirmation. Brain must be included in subsequent tumor assessments if a patient has brain metastases at baseline; otherwise, brain will only be evaluated when clinically indicated.

CT and MRI are the primary imaging modalities. IV contrast should be used unless contraindicated. Oral contrast can be used at the Investigator's discretion. Post-baseline tumor assessments should use the same imaging modality as at baseline. For those patients who have not progressed clinically or radiologically at the time of study drug discontinuation, every effort should be made to continue radiological tumor assessments, utilizing the same imaging modality as used at screening as outlined in the Schedule of Assessments. Patients with bone metastases identified on the baseline bone scan should be followed at scheduled visits using localized CT, MRI, or PET. Patients with known brain metastases should also be followed at scheduled visits using CT or MRI brain, with additional scans performed as clinically indicated (Table 5).

Tumor response criteria will be based on RECIST v1.1 (Eisenhauer, 2009) as cited in Section 17.4. A partial or complete response should be confirmed by a repeat scan (including a bone lesion assessment) not less than 4 weeks from the date the response was first documented per RECIST v1.1.

During the course of this study, scans may be collected and sent/uploaded to the Sponsor or Designee for storage. Centralized storage is intended for possible independent central review (ICR) of disease assessments. At the discretion of the Sponsor, ICR of all scans by RECIST v1.1 may be conducted retrospectively. If needed, guidelines for imaging collection and storage will be provided in a separate document. The clinical management of patients will be based solely upon the results of the assessment conducted by the Investigator based on RECIST v1.1 per protocol.

11.2.1.1. Treatment Beyond Disease Progression during Avelumab Maintenance per RECIST Version 1.1

Evidence indicates some patients treated with immunotherapy may derive clinical benefit after initial evidence of apparent disease progression (Nishino, 2013). Therefore, with approval from the Medical Monitor, avelumab maintenance treatment (with or without trilaciclib) may be continued until loss of clinical benefit, provided the patient appears to be deriving clinical benefit, the Investigator believes it is in the best interest of the patient to continue and the patient has provided re-consent. Treatment past disease progression per RECIST v1.1 should only be considered if a patient is clinically stable and has the following:

- Evidence of clinical benefit as assessed by the Investigator
- Absence of symptoms and signs (including worsening of laboratory values; e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. Decisions to continue treatment beyond initial progression per RECIST v1.1 may be discussed with the Medical Monitor and should be documented in the study records.

Patients with radiographic disease progression confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they continue to meet the criteria above and have evidence of clinical benefit.

Immune-related disease progression (irPD) must be confirmed with worsening of disease bulk on the next tumor assessment, performed at a minimum of 4 weeks after the disease progression by RECIST v1.1 was first noted. If the criteria of worsening disease bulk are met on 2 consecutive scans, the patient is determined to have confirmed irPD. If following an initial progression, the patient has a subsequent immune-related response (immune-related CR, PR, or SD; determined from baseline), then the original progression is not confirmed and the patient may continue to receive study treatment and any subsequent progression must be confirmed on the next consecutive tumor assessment.

Confirmation of progression due to worsening disease bulk is defined as an additional 20% or greater increase in tumor burden volume from the time of initial RECIST v1.1 defined progression (including all target lesions and new measurable lesions) or an unequivocal further increase in nontarget lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

11.2.2. Hematologic Assessments

The myeloprotective effects of trilaciclib administered in patients receiving platinum-based chemotherapy and avelumab maintenance therapy will be evaluated based on the following: kinetics of changes in CBCs (including DSN in chemotherapy Cycle 1 and rate of SN); hematologic toxicities, including febrile neutropenia; RBC and platelet transfusions; hematopoietic growth factor utilization; infections and systemic antibiotic use. All of these variables will be assessed as described in the safety assessments (monitoring of AEs, clinical laboratory assessments, and concomitant medications).

11.3. Safety Assessments

Unless specified otherwise, safety assessments should be conducted prior to study drug administration.

11.3.1. Vital Signs

The following will be collected per the Schedule of Assessments (Table 5):

- Body temperature, pulse rate, blood pressure (diastolic and systolic)
- Height in centimeters (Screening visit only) and body weight in kilograms

Assessments may be performed by a physician, registered nurse, or other qualified health care provider.

11.3.2. Physical Examination

Full physical examination evaluations at Screening should include all major body systems, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations. Subsequent physical exams should be performed as symptoms warrant per Investigator discretion and should include the appropriate body systems (e.g., limited physician exam based on symptoms).

Information about the physical examination must be present in the source documentation at the study site. Clinically relevant findings observed **prior** to the start of study drug, should be recorded as medical history. Clinically relevant findings observed **after** the start of study drug, which meet the definition of an AE, must be recorded on the AE eCRF.

Assessments may be performed by a physician, registered nurse, or other qualified health care provider.

11.3.3. ECOG Performance Status

The Investigator or qualified designee will assess ECOG performance status during the Screening Period to assess for eligibility according to the inclusion and exclusion criteria (Table 13). ECOG performance status will also be assessed per the Schedule of Assessments (Table 5).

Table 14: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group
Oken, 1982.

11.3.4. Electrocardiogram

A single, standard12-lead electrocardiogram (ECG) will be performed in all patients at Screening (Table 5). Additional ECGs may be performed as clinically indicated at any time during the study. All 12-lead ECGs will be obtained after the patient has been resting for at least 10 minutes and shall be recorded at 25 mm/sec. All ECGs for an individual patient shall be recorded with the patient in the same physical position.

The Investigator or qualified designee shall review the ECGs for any abnormalities.

11.3.5. Clinical Safety Laboratory Assessments

Hematology, serum chemistry, and urinalysis will be performed at the site's local certified laboratory per the schedule outlined in the Schedule of Assessments (Table 5). Any consideration for laboratory assessments to be performed at an alternate laboratory outside of the facilities identified for the conduct of the study may impact the integrity of the study data. As such, any such testing should be discussed with the study Medical Monitor and considered as a means to continue appropriate testing for the safety of the patient during COVID-19 restrictions. Clinical laboratory samples may be collected from patients at a different location than Investigator's clinic following approval by the Medical Monitor. A list of clinical laboratory tests to be performed is provided in Section 17.1.

Hematology may be obtained up to 24 hours and serum chemistry and urinalysis may be obtained up to 72 hours prior to each time point on Schedule of Assessments. For women of childbearing potential, pregnancy tests will be performed as follows: serum beta human chorionic gonadotropin (ß-hCG) at Screening and serum or urine ß-hCG on Day 1 of each chemotherapy cycle, Day 1 of every-other avelumab maintenance cycle beginning with the first cycle of avelumab maintenance therapy, and at the End of Treatment Visit. A pregnancy test should be performed within 7 days prior to initiating treatment and must be negative.

Serum chemistry and hematology results shall be reviewed before dosing. Laboratory toxicities will be assessed using the NCI-CTCAE v5.0.

An abnormal laboratory value is not an AE unless it is considered to be clinically significant by the Investigator. Laboratory parameters for which clinically significant values are noted will be re-measured on the appropriate clinical follow-up arranged by the Investigator. Any laboratory value that remains abnormal at the end of the study and that is considered clinically significant should be followed according to accepted medical standards for up to 30 days or until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Medical Monitor notified.

If a subsequent cycle is delayed/skipped for toxicity, the patient should still complete the clinical laboratory assessments on the scheduled Day 1 (entered as an Unscheduled assessment in the eCRF) as well as on the actual first dosing day of that cycle. If the delay is secondary to hematologic toxicity, weekly repeat hematology assessments should continue until the finding meets criteria for resumption of dosing (see Section 9.2; Table 7).

11.3.6. Adverse and Serious Adverse Events

Study-procedure related SAEs will be collected after the ICF is signed; all AEs will be collected starting from the first dose of study drug through the Safety Follow-up Visit. Toxicity will be assessed by Investigators using NCI-CTCAE v5.0.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up, as applicable, AEs that are serious, considered related to the study drugs or study procedures, or that caused the patient to discontinue the study or study drugs (see Section 10.1). Patients should be encouraged to report AEs freely or in response to general, nondirected questioning.

Adverse events (serious and non-serious) should be reported on the appropriate page of the eCRF from the first dose of study treatment through last patient visit.

11.3.6.1. Time Period and Frequency for Collecting Adverse and Serious Adverse Event Information

AEs will be collected starting from the first dose of study drug through the Safety Follow-up Visits at 30 and 90 days. After initiation of study drug, all SAEs and AESIs for avelumab will be reported until 90 days after the last dose of avelumab or initiation of another anti-cancer therapy, whichever occurs first. All other AEs will be reported until 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. Any SAE occurring between the date the patient signs informed consent and the first dose of any study drug, and which the Investigator feels is related to a study specific procedure (i.e., would not have occurred unless the patient was on the study), should also be recorded as an SAE. Any AEs that occur between the date of signing informed consent and the first dose of study drug should be recorded as Medical History.

All SAEs will be recorded and reported to G1 Therapeutics Pharmacovigilance (PVG) or designee immediately and should not exceed 24 hours after becoming aware of the event, as indicated in Section 17.2.

Investigators are not obligated to actively seek AE or SAE information after 90 days following the last dose of study drugs on this study. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator or designee must promptly notify G1 Therapeutics PVG or designee.

11.3.6.2. Method of Detecting Adverse and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 17.2.

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

11.3.6.3. Follow-up of Adverse and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs (both serious and nonserious) will be followed in accordance with good medical practice until resolution, return to baseline, or it is deemed that further recovery is unlikely. All measures required for AE management and the ultimate outcome of the AE will be recorded in the source document and reported to G1 Therapeutics PVG or designee.

All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 10.3). Further information on follow-up procedures is provided in Section 17.2.

11.3.6.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification of G1 Therapeutics PVG or designee by the Investigator (or designee) of an SAE, as described in Section 17.2.4, is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

G1 Therapeutics has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. G1 Therapeutics will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Central IRB/IEC, and Investigators. For all studies, except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and G1 Therapeutics policy and forwarded to Investigators, as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from G1 Therapeutics or designee will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

11.3.6.5. Pregnancy

Details of all pregnancies in female patients will be collected after the start of study intervention and until 5 months after the last dose of avelumab or 6 months after the last dose of gemcitabine, carboplatin, or cisplatin, whichever is longer. Female partners of male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 6 months of the last dose of gemcitabine, carboplatin, or cisplatin, or 4 months after the last dose of trilaciclib, whichever is longer.

If a pregnancy is reported, the Investigator or designee should inform G1 Therapeutics PVG or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 17.3.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

11.4. Pharmacokinetics

Four blood samples for PK analysis of cisplatin will be collected from each patient treated with cisplatin on chemotherapy Cycle 1 Day 1 and one blood sample on chemotherapy Cycle 1 Day 8 (Table 5) as follows: 20-30 minutes after the start of cisplatin infusion, 5-10 minutes prior to end of cisplatin infusion, 1 hour after the end of cisplatin infusion (±15 minutes), 3.5 hours (±30 minutes) after the end of cisplatin infusion, and a single sample on Day 8 prior to dosing of any study drugs. Sites that do not have access to a refrigerated centrifuge should follow the sample processing steps provided in the Study Laboratory Manual.

For those patients randomized to receive trilaciclib, the following blood samples will be collected.

- Five blood samples for PK analysis of trilaciclib and metabolites will be collected from each patient on chemotherapy Cycle 1 Days 1 and 2 (Table 5) as follows: 5-20 minutes

after the start of trilaciclib infusion, within 5 minutes prior to end of trilaciclib infusion, and 25-45 minutes, 4-6 hours, and 18-24 hours after the end of trilaciclib infusion.

- Five blood samples for PK analysis of trilaciclib and metabolites will be collected from each patient on maintenance Cycle 1 Days 1 and 2 and maintenance Cycle 3 Days 1 and 2 (Table 5) as follows: 5-20 minutes after the start of trilaciclib infusion, within 5 minutes prior to end of trilaciclib infusion, and 25-45 minutes, 4-6 hours, and 18-24 hours after the end of trilaciclib infusion.
- One blood sample for PK analysis of avelumab will be collected from each patient on Day 1 of maintenance Cycles 1, 3 and 6 (Table 5) prior to the start of avelumab infusion but after the end of trilaciclib infusion.

The actual date and time of each blood sample collection, the scheduled timepoint of collection, and the time of dose administration prior to the PK sample will be recorded. Details of PK blood sample collection including volume to be collected, timing of samples, processing, storage, and shipping procedures are provided in the Study Laboratory Manual. Do not collect blood for PK samples from the same arm being infused.

11.5. Biomarkers

11.5.1. Rationale for Archival or Fresh Tumor Collection at Screening

In addition to the inclusion criteria requirements, the archival tissue will be used to evaluate in a retrospective fashion the relationship between CDK4/6 status and measures of anti-tumor efficacy as there is a hypothetical risk that trilaciclib could antagonize the intended anti-tumor efficacy of chemotherapy (see Section 4.3). All patients with archival tissue available from their urothelial carcinoma diagnostic sample or fresh biopsy obtained during Screening shall have it sent to a central storage facility for further biomarker evaluation. Tumor tissue must consist of a minimum of 15 slides (preferably 20) or a fixed paraffin block with a depth of at least 75 microns, which includes the tissue needed for PD-L1 evaluations. If archival tissue is not available, a fresh biopsy must be obtained, unless otherwise approved by the Sponsor.

The stored tumor tissue may be used to test for exploratory markers of trilaciclib sensitivity such as genomic profiles, mRNA expression, CDK4/6 dependency, and IHC staining including PD-L1. Additional details regarding tumor tissue collection, processing, handling, and shipping may be found in the laboratory manual. Samples may be stored for up to 10 years if patients sign the consent form and allow their samples to be stored for any future research.

11.5.2. Rationale for Peripheral Blood Collection

For all patients on study, blood samples for biomarkers will be drawn pre-dose on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 3 Day 1, maintenance Cycle 1 Day 1 and maintenance Cycle 3 Day 1 (Table 5).

Chemotherapeutic agents may elicit part of their anti-tumor efficacy by modulating the immune system to enhance antigen presentation, uptake, and processing; prime the immune response through immunodepletion; inhibit regulatory cells; and stimulate immune effector cells (Zitvogel, 2008; McDonnell, 2011; Bracci, 2014). Conversely, immunosuppression from direct cytotoxicity to the bone marrow and immune system over repeated cycles of chemotherapy may

counterbalance the positive immunostimulatory effects of chemotherapy. Therefore, therapeutic approaches to maintain bone marrow health and immune system function should enhance the immune-mediated anti-tumor activity.

Trilaciclib and other CDK4/6 inhibitors have been shown to augment anti-tumor responses in preclinical settings (Klein, 2018) by enhancing T cell activation through modulation of nuclear factor of activated T cell activity (Deng, 2018), as well as increasing antigen presentation through upregulation of major histocompatibility complex class I and II in CDK4/6-sensitive tumors and myeloid cells (Goel, 2017; Schaer, 2018) Additionally, CDK4/6 inhibition can upregulate and stabilize the protein expression of PD-L1 on tumor cells (Zhang, 2018).

To evaluate the impact of trilaciclib administration on chemotherapy-induced changes of the immune system, immunophenotypic changes will be compared from serial peripheral blood samples between patients receiving either trilaciclib or avelumab.

Samples may be stored for up to 10 years if patients sign the consent form and allow their samples to be stored for any future research.

11.6. Anti-Avelumab Antibody and Neutralizing Antibody Testing

Avelumab may elicit an immune response. Patients with signs of any potential immune response to avelumab will be closely monitored.

For patients randomized to receive trilaciclib, one blood sample for the evaluation of avelumab immunogenicity will be collected from each patient on Day 1 of maintenance Cycles 1, 3 and 6 and at the End of Treatment Visit (Table 5). All samples should be drawn within 2 hours before the start of avelumab infusion. All of the samples that are positive for anti-avelumab antibodies may also undergo characterization for neutralizing antibodies.

11.7. Data Monitoring Committee

A DMC will monitor accumulating safety and anti-tumor response data with the first meeting planned for when approximately 10 patients treated with trilaciclib + cisplatin or 10 patients treated with trilaciclib + carboplatin have completed at least 2 cycles of study treatment, whichever occurs first. The meetings will continue approximately every 6 months or as defined in the DMC charter while patients are on study treatment depending upon the enrollment rate. Additional reviews may occur.

A single DMC charter will define the roles and responsibilities of the DMC and its members. Additional details regarding the committee's composition, scope, objectives, procedures, and policies, including the associated analysis plan and data to be reviewed for the Sponsor, Investigators, and patients, are described in the DMC charter. The DMC will monitor accumulating safety and disposition data entirely independent of the conduct of the study.

11.8. End of Treatment Visit

When a patient permanently discontinues study treatment, the patient should complete an End of Treatment Visit from last dose of study drug as outlined in Table 5.

11.9. Safety Follow-up Visit

The patient should complete a Safety Follow-up Visit 30 days (+7 days) from the last dose of study drug and 90 days (±7 days) from last dose of avelumab as outlined in Table 5. The safety follow-up visit 90 days (±7 days) from last dose of avelumab may occur at the study site or can be via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

11.10. Survival Follow-up

After completion of the End of Treatment Visit, the patient will be followed for survival approximately every 3 months (±7 days) (including an assessment at Month 17 Day 1 [±7days]). Survival Follow-up Visits may be done via telephone, email, or clinic visits.

Information will be collected until the end of the study (or death) to record the patient's status (alive or dead). In addition, details of any subsequent systemic anti-cancer therapy initiated, including name(s) of agent(s), dates (start/stop) administered, best response to the treatment, and date of progression should also be reported in EDC to the best of their ability. Provided that the patient has not withdrawn consent for follow-up contact, information from medical records may be substituted for phone or other contact, provided that records are available as source documentation. Public records may be used to verify survival status if permitted by institutional or country guidances.

12. STATISTICAL CONSIDERATIONS

Full details on the statistical analyses to be performed will be provided in a separate statistical analysis plan (SAP).

12.1. Sample Size Determination

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

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

12.2. Analysis Population

The following analysis populations are defined for the study.

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

The response evaluable (RE) population includes all patients who are in the ITT population and who have measurable (target) tumor lesion(s) at the baseline tumor assessment and either (i) have at least 1 post-baseline tumor assessment, or (ii) do not have post-dose tumor assessment but have clinical progression as noted by the Investigator, or (iii) died due to disease progression prior to their first post-baseline tumor scan. Analyses using this analysis population will be conducted according to the randomly assigned treatment. The RE population will be the primary analysis set for tumor response analyses.

The safety population includes all randomized patients who received at least 1 dose of study drug. Analyses using the safety population will be conducted according to the actual treatment received. All safety analyses will be evaluated using the safety population.

The PK population will include all patients who received at least one dose of trilaciclib or cisplatin or avelumab and have evaluable PK data.

12.3. Time of Planned Analysis

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

The first planned analysis will be conducted when all randomized patients have either completed chemotherapy or discontinued during the chemotherapy period. Trilaciclib's effect on ORR during the chemotherapy period will be evaluated in this analysis.

In addition, myelosuppression endpoints and safety data collected during the chemotherapy period will be performed at this time.

12.3.2. Intermediate Planned Analyses – Analyses for Progression Free Survival and Probability of Survival at Month 16

The intermediate planned analyses will evaluate the effect of trilaciclib on PFS (the primary endpoint) and the survival probability at Month 16. The timing to perform each analysis is conditional on the respective events. When the pre-specified condition for a given endpoint is met, the analysis for that endpoint will be performed. Therefore, these analyses could happen concurrently or separately.

- PFS. The analysis for PFS will be conducted at the time when 63 patients have radiographic determined disease progression or died.
- Probability of survival at Month 16. This analysis will be performed when all randomized patients have either completed the survival assessment at Day 1 of Month 17 or discontinued prior to the that visit.

12.3.3. Final Planned Analysis – Analyses for Overall Survival

Analysis for OS will be conducted when approximately 60% randomized patients have died (i.e., 54 deaths). Study database will be locked to perform the final OS analysis and other SAP specified analyses, including the following analyses:

- Analysis of tumor response endpoints (ORR, DCR, and DOR) in the overall study on the pooled data from both the chemotherapy and maintenance periods.
- Analysis of tumor response endpoints (ORR and DCR) during the maintenance period.
- Analysis of safety data from the maintenance period.
- Analysis of anti-tumor endpoints during the overall study by CDK4/6 biomarker signature status and by PD-L1 subgroup as described in Section 12.4.8 .

12.4. Statistical Analysis Methods

An SAP will be developed and finalized prior to the first planned analysis and will include more details related to the statistical analysis of this study's data. This section is a summary of the key aspects of the planned statistical analyses.

12.4.1. General Considerations

All statistical analyses will be performed using SAS® v9.4 or higher. Categorical variables will be summarized by counts and percentages, while continuous variables will be summarized by mean, standard deviations, median, 25% and 75% percentiles, and minimum and maximum values by treatment group.

Patients will be randomized according to the two stratification factors: presence of visceral metastasis (yes or no), and choice of initial platinum-based chemotherapy (cisplatin or carboplatin). When appropriate, these two stratification factors will be included in statistical models for efficacy analyses with the strata information as entered in IWRS at the time of randomization.

12.4.2. Patient Disposition

Patient disposition will be summarized separately for all patients by treatment group and overall. The summary will include the following: number of all screened patients; number and percentage of patients that were randomized, received study drug, and discontinued from each study drug, as well as the reasons for study drug discontinuation; and reasons for study discontinuation.

12.4.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized separately for the ITT population by treatment group and overall. The summary will include age, age groups, gender, race, ethnicity, screening vital signs (body weight, height, BMI, BSA), ECOG status (0-2), PD-L1 status (positive or negative), visceral metastasis (yes or no) at, and initial platinum-based chemotherapy administered (cisplatin or carboplatin).

12.4.4. Prior and Subsequent Anticancer Therapies

Prior and subsequent anticancer therapy verbatim terms will be coded to Anatomical Therapeutic Classification and preferred term using the latest version of World Health Organization-Drug Dictionary. For the ITT population, summary statistics will be provided for prior and subsequent systemic anti-cancer therapies by treatment group and overall. For the subsequent systemic anti-cancer therapies, the lines of therapy, best response to each treatment regimen, and disease progression status will also be summarized by treatment group and overall.

12.4.5. Study Drug Exposure, Modification, and Dose Intensity

The summary described below will be based on the safety population.

Duration of study drug exposure will be defined for each chemotherapy drug (gemcitabine, cisplatin or carboplatin) and for trilaciclib or avelumab and summarized by treatment group.

For each treatment group, the number of cycles that patients have received will be summarized by descriptive statistics as a continuous variable, while the number of cycles that are completed will be summarized as a categorical variable.

Study drug modifications will be summarized by treatment group in three categories: chemotherapy dose reductions, chemotherapy cycle delay, and infusion interruption. The number and percentage of patients who have any chemotherapy dose reductions and have at least one

dose reduction for a particular chemotherapy will be summarized along with a summary of the number of dose reductions for each chemotherapy; the number and percentage of patients who have at least one cycle delay will be summarized along with a summary of the number of cycles that have been delayed; the number and percentage of patients who have at least one infusion interruption for trilaciclib, avelumab, or any chemotherapy will be summarized along with a summary of the number of interruptions. Lastly, the primary reason for each form of study drug modification (chemotherapy dose reductions, cycle delay, and infusion interruption) will also be summarized by treatment group.

For trilaciclib, avelumab, gemcitabine, cisplatin or carboplatin, cumulative dose, dose intensity, relative dose, and relative dose intensity will be derived and summarized by treatment group, respectively,

12.4.6. Efficacy Analyses

12.4.6.1. Analyses of Primary Efficacy Endpoint –Progression Free Survival during the Study

The primary efficacy endpoint PFS (months) during the overall study is defined as the time from the date of randomization to the date of documented radiologic disease progression per RECIST v1.1 or death due to any cause, whichever comes first regardless of in which treatment period of the event occurs. Progression-free survival will be determined using all data until the last evaluable visit prior to or on the date of (i) radiographic disease progression per RECIST v1.1; (ii) withdrawal of consent to obtain additional scans on study; or (iii) initiation of subsequent anticancer therapy, whichever is earlier. Death (in absence of PD) is always categorized as an event in the PFS analysis. Censoring rules for patients who do not experience PD or death at the data cutoff date will be described in the study SAP.

The primary analysis for PFS will be conducted at the time when 63 patients have radiographic determined disease progression or died. The treatment effect on PFS will be primarily evaluated using a stratified log-rank test accounting for the two stratification factors. The magnitude of the treatment effect will be estimated by hazard ratio (HR) (Arm B versus Arm A) using a stratified Cox proportional hazards model controlling for the two stratification factors. The 80% confidence interval (CI) will be generated for the HR. The Kaplan-Meier plots will be produced for each treatment group. The within-group median, 25%, and 75% percentile of PFS will be estimated using the Kaplan-Meier method with their corresponding 95% CI calculated using the method by Brookmeyer and Crowley (1982). The number and percentage of patients who do not have progressive disease ≥1 year after randomization will be summarized by treatment group.

Analysis of PFS during the study will be based on the ITT population.

12.4.6.2. Analysis for Secondary Anti-tumor Efficacy Endpoints

Secondary anti-tumor endpoints include the following:

- Tumor response related endpoints for chemotherapy period maintenance period and during the overall study
  - Objective response rate (ORR) in the chemotherapy and maintenance periods, and during the overall study

- Disease control rate (DCR) in the maintenance period and during the overall study
- Duration of objective response (DOR) during the overall study

- Progression free survival (PFS) in the maintenance period
- Probability of survival at Month 16 and Overall Survival (OS) in the maintenance period and during the overall study

Analysis for Tumor Responses

At each tumor assessment visit, an overall time point response by RECIST v1.1 will be derived programmatically using the measurements provided by the Investigator for target lesions, non-target lesions, and new lesions collected in the eCRF. Best overall response (BOR) will be determined using all visit responses prior to or on the date of (i) radiographic disease progression; (ii) withdrawal of consent to obtain tumor scans; (iii) death; (iv) lost to follow-up; or (v) initiation of subsequent anticancer therapy, whichever is earlier.

The number and percentage of patients in each category of derived BOR (confirmed or unconfirmed CR, confirmed or unconfirmed PR, SD, PD, or Not Evaluable) will be summarized. For all tumor response endpoint analyses, unconfirmed CR or PR will be only allowed if there is lack of time to perform confirmed tumor scan in the period of chemotherapy before the patient entering the maintenance period.

ORR will be evaluated at the time when all randomized patients have finished chemotherapy and at the end of the treatment period. ORR in the chemotherapy period is defined as the proportion of patients with BOR of confirmed or unconfirmed CR or PR. ORR in the maintenance period is defined as the proportion of patients with BOR of confirmed CR or PR during maintenance period. ORR in the overall study is defined as the proportion of patients with BOR of confirmed CR or PR as determined using all tumor scan data from both chemotherapy and maintenance periods. 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 stratified Cochran–Mantel–Haenszel (CMH) method to account for the two stratification factors. The adjusted proportion difference (Arm B – Arm A) and its 95% CI will be calculated using CMH weight (as described in Kim, 2013). ORR will be analyzed based on the RE population.

DCR is defined as the proportion of patients with BOR of CR, or PR (confirmed), or SD lasting at least 24 weeks, as appropriate to each study period as described for ORR. The analysis of DCR will be performed using the methods similarly to ORR.

Duration of objective response is the time between first objective response of CR or PR (confirmed), as appropriate to each treatment period as described for ORR, and the first date that progressive disease is documented or death, whichever comes first. DOR will only be analyzed for the patients who have achieved objective response. For patients with objective response but did not reach radiographically determined PD or died, the last adequate tumor assessment date prior to the earliest time of the following will be used to calculate censored time: (i) withdrew consent to obtain scans; (ii) lost to follow-up; (iii) initiated subsequent anticancer therapy. The Kaplan-Meier method will be used to estimate the median, 25%, and 75% percentile of DOR for each treatment group, along with the 95% CI, which is calculated using the method by Brookmeyer and Crowley (1982).

Analysis for PFS in the maintenance period

In addition, PFS in the maintenance period is defined as the time from the date of entering the maintenance period to the date of documented radiologic disease progression per RECIST v1.1 or death due to any cause, whichever comes first in that period. The PFS in maintenance period will be analyzed using the statistical methods as used for the analysis for PFS during the study.

Analysis for OS

Overall survival during the overall study is defined as the time (months) from the date of randomization to the date of death for patients who died in the study due to any cause or the time to the last contact date known to be alive for those who survived as of the data cutoff date for the planned OS analysis (censored cases). For patients who drop out of the study right after randomization, their survival time is censored at the date of randomization. In addition, OS in the maintenance period will also be analyzed. For OS in the maintenance period, the date of entering the maintenance period is used as the start time in the OS calculation. The treatment effect on OS will be evaluated by applying the same statistical model used for the PFS analysis. The number and percentage of patients who survive ≥ 1 year after randomization will be summarized by treatment group. Survival distribution of OS will be based on Kaplan-Meier method used for the analysis for PFS. The survival probability at Month 16 will be estimated using Kaplan-Meier method along with its two-sided 95% CI (Kalbfleisch, 1980) for each treatment group. In addition, the number and percentage of patients who died or censored will be summarized along with the eCRF collected reasons for death by treatment group. The total duration of follow-up will also be summarized by treatment group.

The analysis for OS during the study will be based on the ITT population while the analysis for PFS and OS in the maintenance period will be based on the ITT population with at least a visit in the maintenance period.

The analysis for ORR, DCR and DOR during the study and ORR in the chemotherapy will be based on the RE population while the analysis for ORR and DCR in the maintenance period will be based on the RE population with at least a visit in the maintenance period.

12.4.6.3. Analysis of Myelosuppression Endpoints

Myelosuppression endpoints are grouped by lineage and consequence of chemotherapy-induced myelosuppression (CIM) as follows:

- Neutrophils related (including DSN in Cycle 1, occurrence of SN, occurrence of FN, and occurrence of G-CSF administration)
- RBC related (including occurrence of Grade 3/4 decrease of hemoglobin, occurrence and number of RBC transfusions on/after Week 5, and occurrence of ESA administration)
- Platelet related (including occurrence of Grade 3/4 decrease of platelets, occurrence and number of platelet transfusions)
- Endpoints related to trilaciclib's effect on chemotherapy dosing or hospitalizations due to chemotherapy-induced myelosuppression (including occurrence and number of dose reductions, or dose delay, and occurrence and number of hospitalizations due to CIM)

The analysis of myelosuppression endpoints will be based on the ITT population.

Continuous Myelosuppression Endpoint: DSN in Cycle 1

For patients with at least one SN event (ANC value <0 .5 × 10^9/L) in Cycle 1, DSN (days) in Cycle 1 is defined as the number of days from the date of the first ANC value of <0.5 × 10^9/L observed at Cycle 1 to the date of the first ANC value ≥0.5 × 10^9/L and no other ANC values <0.5 × 10^9/L occurred between this day and end of Cycle 1. DSN will be set to 0 for patients who do not experience SN in Cycle 1. Data from both scheduled and unscheduled assessments will be included. The actual assessment date, rather than visit date, will be used in the derivation of DSN in Cycle 1.

The treatment effect on DSN in Cycle 1 will be evaluated using nonparametric analysis of covariance (ANCOVA) (Quade, 1967). In this analysis, the rank-transformed (within each stratum) DSN values are analyzed by an ANCOVA model with the terms of treatment and the two stratification factors as fixed effects and the rank-transformed baseline ANC (within each stratum) as a covariate. In addition, the mean difference (Arm B – Arm A), the standard error and the 95% CI for the difference generated from a Satterthwaite t-test will be presented.

Binary Myelosuppression Endpoints:

For the binary myelosuppression endpoints (e.g., the occurrence of SN and the occurrence of RBC transfusions on/after Week 5), the number and percentage of patients with at least one occurrence during the treatment period will be summarized by treatment group. The treatment effect will be evaluated using the modified Poisson regression model (Zou, 2004). The model will include the treatment and the two stratification factors as the fixed effect and corresponding baseline as a covariate when applicable (e.g., baseline ANC for occurrence of SN, and baseline hemoglobin for RBC transfusions on/after Week 5). The log-transformed duration of exposure either in week or in cycle will be used as the offset in the model to account for the variable duration for each patient (e.g., the number of cycles for occurrence of SN, and the number of weeks for RBC transfusions on/after Week 5). A 2-sided p-value, adjusted relative risk (aRR) (Arm B versus Arm A) and their 95% CIs will be calculated.

Counting Myelosuppression Endpoints:

For the counting myelosuppression endpoints (e.g., the number of RBC transfusions on/after Week 5, and the number of dose reductions during the treatment period), the total number of the event, the total number of exposure (either in the unit of week or cycle), and event rate per 100 weeks or cycles will be summarized by treatment group. For example, the event rate for RBC transfusions on/after Week 5 will be reported by 100 weeks and that for dose reduction will be reported by 100 cycles. For a given event, patients without any of the event during the treatment period will be assigned a value 0 to be included in the analysis. The treatment group difference in the event rate will be assessed by a negative binomial model. The model will include the treatment and the two stratification factors as the fixed effect with corresponding baseline value as a covariate when applicable (e.g., baseline hemoglobin for the analysis of number of RBC transfusions on/after Week 5). The log-transformed duration of exposure in week or in cycle will be used as the offset in the model to account for the variable duration for each patient (e.g., number of weeks for RBC transfusions on/after Week 5, and number of cycles for dose reduction). A 2-sided p-value, aRR (Arm B versus Arm A) and its 95% CI will be generated from the statistical model as applied.

12.4.7. Safety Analyses

Safety and tolerability will be assessed by AEs, laboratory tests, and vital signs. All safety data will be summarized using descriptive statistics by treatment group using the safety population. Data collected through scheduled or non-scheduled visits will all be included in the safety analyses.

Safety data collected from the chemotherapy period and from the chemotherapy maintenance period will be summarized separately.

12.4.7.1. Adverse Events

AEs are defined as those events occurring or worsening after treatment has begun on this study. Adverse event data will be coded to system organ class and preferred term using the latest version of MedDRA. The severity (toxicity grades 1-5) of AEs will be graded by Investigators according to the NCI-CTCAE Version 5.0. The number and percentage of patients experiencing any AE overall, will be tabulated for each treatment group, and broken down as well by system organ class, preferred term, and CTCAE grade. Adverse events considered by the Investigator to be related to treatment will also be summarized by the treatment to which it is attributed (e.g., trilaciclib/avelumab, chemotherapy) for each treatment group. Severity of AEs will be tabulated based on the greatest severity observed for each patient. In the tabulation of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be used in a summary. AESIs for trilaciclib, AESIs for avelumab, AEs leading to study drug discontinuation, dose reductions, cycle delays, and use of concomitant medications to treat AEs will be tabulated separately.

12.4.7.2. Other Safety Endpoints

Observed values and changes from baseline in vital signs and laboratory assessments of hematology, serum chemistry, and liver function parameters will be summarized by treatment group for each scheduled visit, maximum and minimum post-baseline by cycle, overall maximum and minimum post-baseline during treatment period, and last on-treatment assessment.

Serum chemistry and hematology laboratory parameters will be characterized according to CTCAE toxicity grade from 1 to 5, Version 5.0, when possible. The number and percentage of patients within each CTCAE grade will be summarized for the overall treatment period as well as for each cycle. If a patient has multiple laboratory assessments in an interval of interest, the maximum grade will be reported.

For vital signs potentially clinically significant (PCS) findings will be summarized by treatment group. The potentially clinically significant vital signs are defined either by post-baseline assessment or by the change from baseline with respect to the pre-specified thresholds. The criteria defining PCS for vital signs will be detailed in the study SAP.

12.4.8. Exploratory Analyses

Differences in pharmacodynamic parameters in tumor and peripheral blood including those relating to immune-based mechanisms will be summarized.

The number and percentage of patients in different CDK4/6 signature status (i.e., CDK4/6 independent, CDK4/6 dependent, and CDK4/6 indeterminate) will be summarized by treatment

group. Selected anti-tumor endpoints (PFS, ORR, and OS during the overall study) will be evaluated by subgroup of patients with different CDK4/6 signature status. Within each type of signature, the analysis methods for PFS, ORR, and OS during the overall study will follow the approaches outlined in Section 12.4.6.2.

Anti-tumor endpoints of PFS, OS, ORR, DOR and DCR during the study will be evaluated by subgroup of patients with different PD-L1 status. Within each subgroup, the analysis methods for these anti-tumor endpoints will follow the approaches as outlined in Section 12.4.6.2.

12.4.9. Pharmacokinetic Analyses

The PK of trilaciclib and metabolites, cisplatin, and avelumab will be determined using a non-linear mixed effects modeling approach. Relevant population pharmacokinetic parameters will be estimated and reported. Details of population pharmacokinetic analyses will be described in the population pharmacokinetic/pharmacodynamic analysis plan.

12.4.10. Pharmacokinetic/Pharmacodynamic Analyses

If data warrant, exploratory analyses may be performed to examine the relationship(s) between exposure to trilaciclib and pharmacodynamic endpoints or other efficacy and safety endpoints. Details of population PK/pharmacodynamic analyses will be described in a separate population PK/pharmacodynamic analysis plan.

13. ETHICS

13.1. Ethics Review

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), International Council for Harmonisation (ICH) guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

13.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or the patient's legally authorized representative where allowed by local regulation.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

14.2. Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or Designee electronically. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or Designee is responsible for the data management of this study including quality checking of the data.
- Study Monitors will perform ongoing source data verification at the frequencies and SDV extent as outlined in the Monitoring Plan to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the investigation of trilaciclib. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation

relating to the study, the Investigator must permit access to such records. No records may be destroyed during the retention period without the written approval of the Sponsor. No records maybe transferred to another location or party without written notification to the Sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

A study-specific COVID-19 Assessment Plan will be utilized for any necessary modifications and/or mitigation to the data collection, monitoring or other associated activities during this study due to the COVID-19 pandemic.

14.3. Dissemination of Clinical Study Data

The Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov, the EudraCT, and other public registries in accordance with appliable local laws/regulations.

Data results are posted in an objective, accurate, balanced, and complete manner. Results are posted regardless of outcome of the study.

14.4. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. All data reported in the eCRF should be supported by source documents; direct entry of data into the eCRF is not permitted in this study.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

14.5. Audits and Inspections

Authorized representatives of G1 Therapeutics, a regulatory authority, an IEC, or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact G1 Therapeutics immediately if contacted by a regulatory agency about an inspection.

15. PUBLICATION POLICY

By signing the study protocol, the Investigator and his or her institution agree that the results of the study may be used by G1 Therapeutics, Inc. for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

Initial publication of the results of this study will be of a cooperative nature that may include authors representing the Sponsor, Investigator(s), and collaborating scientists. Independent publications by involved individuals may follow. Investigators and their institutions agree not to publish or publicly present any interim results of studies without the prior written consent of G1 Therapeutics, Inc. G1 Therapeutics, Inc. reserves the right to request modification of any publication, presentation or use by the Investigator if such activity may jeopardize a patent application, an existing patent, or other proprietary rights. G1 Therapeutics, Inc. shall determine order of authorship of any publication combining all clinical results of this study.

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17. APPENDICES

17.1. Clinical Laboratory Tests

- The timing and laboratory tests detailed in Schedule of Assessments (Table 5) will be performed by a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 7 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations

Table 15: Protocol-Specified Safety Laboratory Assessments

Laboratory Assessment	Parameters		
Hematology	Absolute neutrophil count	Hemoglobin	Platelets
	Hematocrit	Lymphocytes	WBC
Serum Chemistry	Alanine Aminotransferase (ALT)	Calcium	Serum Creatinine
	Albumin	Chloride	Sodium
	Alkaline phosphatase	Glucose	Thyroid Stimulating Hormone (TSH)
	Aspartate Aminotransferase (AST)	Magnesium	Thyroxine (T4, free)
	Bicarbonate	Phosphate (inorganic)	Total Bilirubin
	Blood Urea Nitrogen (BUN) or Urea	Potassium	Total Protein
Urinalysis	Semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin		
	Microscopic examination (including RBC, WBC, and casts) will be performed, if clinically warranted		
Other Tests	Serum or urine human chorionic gonadotropin (hCG) pregnancy test (for WOCBP only)		

hCG=human chorionic gonadotropin; RBC=red blood cell; WBC=white blood cell; WOCBP=woman of childbearing potential

17.2. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

17.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant and require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease) unless they are associated with an already reported clinical event, e.g. elevated liver enzymes in a patient with jaundice. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

17.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

17.2.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to G1 Therapeutics (or designee) in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by G1 Therapeutics (or designee). In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to G1 Therapeutics (or designee).
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- All SAEs should be reported to G1 Therapeutics PVG (or designee) within 24 hours of notification on an SAE Form in the eCRF. Any relevant source data related to the SAE that cannot be entered in the EDC should be emailed or faxed to G1 Therapeutics PVG (or designee):

  G1 Therapeutics Pharmacovigilance
  Email: safetyreporting@g1therapeutics.com
  Fax: +1-984-285-7131

Assessment of Intensity

Intensity will be assessed using NCI-CTCAE v5.0 criteria, as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

AE and SAE Recording

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE (Related or Not Related); i.e., is there a "reasonable possibility" the study intervention caused the event (yes/no).
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to G1 Therapeutics PVG (or designee). However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to G1 Therapeutics PVG (or designee).
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by G1 Therapeutics PVG (or designee) to elucidate the nature and/or causality of the SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any new or updated SAE data to G1 Therapeutics PVG (or designee) within 24 hours of receipt of the information:

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

17.2.4. Reporting of SAEs

SAE Reporting to G1 Therapeutics (or designee) via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to G1 Therapeutics (or designee) will be the EDC.
- If the electronic system is unavailable, then the site will use the paper SAE Report Form in order to report the event within 24 hours via email or fax (see below for SAE reporting contact information).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site should report this information on a paper SAE Report form or notify the Medical Monitor by telephone.
- Contact for SAE reporting:

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

17.3. Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential Definition

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes), additional evaluation should be considered.

Women in the following categories are not considered Woman of Childbearing Potential

1. Premenarchal

   Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

2. Premenopausal female with 1 of the following acceptable surgical sterilization techniques: complete or partial hysterectomy, bilateral tubal ligation, or occlusion with surgery at least 6 months prior to dosing, or bilateral oophorectomy with surgery at least 2 months prior to dosing.

3. Postmenopausal female: defined as spontaneous amenorrhea for > 12 months prior to Screening without alternative cause (e.g., implantable contraceptive, side effect of medication, etc.) and a serum follicle stimulating hormone (FSH) within the laboratory's reference range for postmenopausal females.

   - Women taking hormone replacement therapy (HRT) must discontinue HRT at least 2-4 weeks prior to Screening for accurate assessment of FSH (though exact interval will depend on the type and dosage of HRT and should be determined by the principal Investigator).

Contraception Guidance

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Male patients: Males must be surgically sterile prior to Screening with appropriate documentation (absence of sperm in ejaculate 6 months after procedure) or have a female partner(s) who is either postmenopausal, surgically sterile, or using 2 forms of concurrent contraception as defined below. In addition, males must also refrain from sperm donation during the study and utilize a barrier method with intercourse during and for 6 months following discontinuation of treatment.

- Female patients: All females of childbearing potential must have a negative serum β-hCG test result at screening, and negative serum pregnancy test within 7 days of starting study treatment and at the End of Treatment Visit.

- Females must be either postmenopausal, surgically sterile, or agree to use 2 concurrent forms of contraception during the study and for 6 months following last dose of study drug. Acceptable forms of contraception include:

  - Established use of oral, injected or implanted hormonal methods of contraception (stable dose at least 3 months prior to dosing)
  - Intrauterine device or intrauterine system
  - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Barrier methods alone (without spermicide) are not acceptable methods. Likewise, spermicide alone is not an acceptable method
  - Male sterilization prior to Screening with the appropriate post-vasectomy documentation (absence of sperm in the ejaculate 6 months after procedure). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
  - True abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- For patients who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a patient who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously. If a patient who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described above.

In addition, patients are to comply with the following guidelines:

- For women: Contraceptive use is required during the Treatment Phase and for at least 6 months after the last dose of carboplatin, cisplatin, or gemcitabine or for 1 month after the last dose of avelumab or trilaciclib.
- For men: Contraceptive use is required during the Treatment Phase and for at least 6 months after the last dose of carboplatin, cisplatin, or gemcitabine.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator or designee will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to males who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator or designee will record pregnancy information on the Pregnancy – Initial Report Form and submitted to G1 Therapeutics PVG or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. The Pregnancy – Follow-up Report Form should be used to report information on the status of the mother and child and will be forwarded to G1 Therapeutics PVG or designee. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Contact for Pregnancy reporting:

G1 Therapeutics Pharmacovigilance

Email: safetyreporting@g1therapeutics.com

Fax: +1-984-285-7131

Female Patients who become pregnant

- The Investigator or designee will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial Information will be recorded on the Pregnancy Reporting and Outcome Form (Pregnancy – Initial Report Form) and submitted to G1 PVG or designee within 24 hours of learning of a patient's pregnancy within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator or designee will collect follow-up information on the patient and the neonate and the information will be collected on the Pregnancy – Follow-up Report Form and forwarded to G1 Therapeutics PVG or designee. Generally, follow-up will not be required for longer than 6 to 12 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to G1 Therapeutics PVG or designee. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention.

  Contact for Pregnancy reporting:

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

17.4. Definitions of Tumor Response and Disease Progression (per RECIST v1.1)

The determination of tumor response and progression will be based on the RECIST v1.1 (Eisenhauer, 2009). Disease progression may also be determined clinically by the Investigator. Tumor lesions will be categorized as follows:

Measurable lesions: tumor lesions with a longest diameter (measured in at least 1 dimension) with a minimum size as follows:

- 10 mm by CT or MRI (with a scan slice thickness of no greater than 5 mm)
- Measurable lymph nodes must be ≥15 mm on the short axis by CT or MRI (with a scan slice thickness of no greater than 5 mm); only the short axis is to be measured at baseline and follow-up.
- Lytic bone lesions or mixed lytic-blastic lesions with a soft tissue component meeting the definition of measurability above can be considered measurable lesions.
- Cystic lesions representing cystic metastases that meet the definition of measurability described above can be considered measurable lesions. If present, noncystic lesions should be selected as target lesions for this study.
- A tumor lesion that has been previously irradiated may be considered measurable if unequivocal growth of the lesion has been demonstrated.

Target lesions: At baseline, up to 5 measurable tumor lesions/lymph nodes (with a maximum of 2 lesions per organ) should be identified as target lesions. Lesions with the longest diameter, that are representative of all involved organs, and for which reproducible repeated measurements can be obtained should be selected as the target lesions. Malignant lymph node is considered an organ in this study, therefore only 2 malignant lymph nodes (regardless of location) may be selected as target lesions and all others should be entered as nontarget lesions.

Non-measurable Lesions: tumor lesions with a longest diameter <10 mm, lymph nodes with ≥10 to <15 mm short axis, or non-measurable lesions such as leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by CT scan or MRI.

Nontarget lesions: All other lesions (or sites of disease) identified at baseline should be identified as nontarget lesions and recorded in the eCRF. Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each nontarget lesion should be recorded in the eCRF at each follow-up time point. Multiple nontarget lesions in the same organ may be noted as a single item on the eCRF.

Evaluation of Target Lesions

The definitions for tumor response for the target lesion per RECIST v1.1 are as follows:

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. 'Unequivocal progression' represents a substantial increase in overall tumor burden such that treatment should be discontinued even in the setting of SD or PR in the target disease. Although a clear progression of "non-target" lesions only is rare, the opinion of the treating physician should prevail in such circumstances.

Appearance of New Lesions

The appearance of new lesion(s) is considered PD according to RECIST v1.1.

Timepoint Response

Patients with Measurable Disease (i.e., Target ± Non-Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-CR/Non-PD/NE	No	PR
SD	Non-CR/Non-PD/NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD[a]	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; NE=not evaluable; PD: progressive disease; PR=partial response; SD=stable disease.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.
[a] Unequivocal progression in non-target lesions may be accepted as disease progression.

Patients with Evaluable or Non-Measurable Disease Only (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response; NE=not evaluable; PD: progressive disease; SD=stable disease.

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

17.5. Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study (see Section 7.2 for specific exceptions). Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Acute disseminated	Interstitial cystitis
Encephalomyelitis	Kawasaki's disease
Addison's disease	Lambert-Eaton myasthenia syndrome
Ankylosing spondylitis	Lupus erythematosus
Antiphospholipid antibody syndrome	Lyme disease - chronic
Aplastic anemia	Meniere's syndrome
Autoimmune hemolytic anemia	Mooren's ulcer
Autoimmune hepatitis	Morphea
Autoimmune hypoparathyroidism	Multiple sclerosis
Autoimmune hypophysitis	Myasthenia gravis Neuromyotonia
Autoimmune myocarditis	Opsoclonus myoclonus syndrome
Autoimmune oophoritis	Optic neuritis
Autoimmune orchitis	Ord's thyroiditis
Autoimmune thrombocytopenic purpura	Pem phigus
Behcet's disease	Pernicious anemia
Bullous pemphigold	Polyarteritis nodusa
Chronic fatigue syndrome	Polyarthritis
Chronic inflammatory demyelinating	Polyglandular autoimmune syndrome
Polyneuropathy	Primary biliary cirrhosis
Chung-Strauss syndrome	Psoriasis
Crohn's disease	Reiter's syndrome
Dermatomyositis	Rheumatoid arthritis

Diabetes mellitus type 1	Sarcoidosis
Dysautonomia	Scleroderma
Epidermolysis bullosa acquista	Sjögren's syndrome
Gestational pemphigoid	Stiff-Person syndrome
Giant cell arteritis	Takayasu's arteritis
Goodpasture's syndrome	Ulcerative colitis
Graves' disease	Vitiligo
Guillain-Barré syndrome	Vogt-Kovanagi-Harada disease
Hashimoto's disease	Wegener's granulomatosis
IgA nephropathy	
Inflammatory bowel disease	