Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy

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I have read and understand the contents of this clinical protocol for Study G1T28-04 (Version 4.0) dated 31 August 2017 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 this study.

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By signing below, the investigator agrees to adhere to the protocol as outlined.

Principal Investigator:

Principal Investigator Signature	Date
Principal Investigator Name	Institution

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1.1. List of In-Text Tables

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{Nadir}	area under the concentration-time curve from predose to nadir
BCRP	breast cancer resistance protein
BED	biologically effective dose
β-hCG	beta human chorionic gonadotropin
bpm	beats per minute
BSA	body surface area
BSEP	bile salt export pump
CBC	complete blood count
CD3	cluster of differentiation 3
CD8	cluster of differentiation 8
CDK2/4/6	cyclin-dependent kinase 2/4/6
CFR	Code of Federal Regulations
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D5W	dextrose 5% in water
DDI	drug-drug interaction
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EdU	5 ethynyl-2'-deoxyuridine

Abbreviation	Definition
EOI	end of infusion
ER	estrogen receptor
CCI [redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose
FOXP3	forkhead box P3
G_1	gap 1 phase of the cell cycle
G_2	gap 2 phase of the cell cycle
G1T28	trilaciclib; formerly G1T28-1
GC	gemcitabine and carboplatin
GC therapy	gemcitabine and carboplatin on Days 1 and 8 of 21-day cycles
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
γH2AX	phosphorylated histone H2AX
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HSPC	hematopoietic stem and progenitor cell
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	independent ethics committee
IHC	immunohistochemistry
IRB	institutional review board
IV	intravenous
LD	longest diameter
LS	least square
M	mitosis phase of cell cycle
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
MDR1	p-glycoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRP1 or 2	multidrug resistance protein 1 or 2
NCI	National Cancer Institute
NE	not evaluable
NYHA	New York Heart Association

Abbreviation	Definition
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
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
CCI	[redacted]
CCI	[redacted]
Rb	retinoblastoma protein
RB	retinoblastoma gene
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RH	relative humidity
CCI	[redacted]
S	synthesis phase of cell cycle in which DNA is replicated
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SOP	standard operating procedure
$t_{1/2}$	terminal half-life
T_{max}	time to reach C_{max}
TNBC	triple negative breast cancer
ULN	upper limit of normal
Vz	volume of distribution in the terminal elimination phase
WBC	white blood cell

3. SYNOPSIS

Title	Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy
Study Rationale	Chemotherapy-induced myelosuppression continues to represent the major dose-limiting toxicity (DLT) of cytotoxic chemotherapy and can be manifested as neutropenia, lymphopenia, anemia, and/or thrombocytopenia. As such, myelosuppression is the source of many important side effects of cancer treatment, such as infection, sepsis, bleeding, and fatigue, leading to the need for hospitalizations, growth factor support, and transfusions (red blood cells [RBCs] or platelets). Moreover, clinical concerns raised by myelosuppression commonly lead to chemotherapy dose reductions and limit therapeutic dose intensity. In addition to the side effects of chemotherapy, chemotherapy-induced immunosuppression may limit antitumor efficacy due to an inability of the host immune system to effectively mount a response against the cancer. Therefore, preserving the bone marrow and immune system from the cytotoxic effects of chemotherapy has the potential to maximize the antitumor activity of chemotherapy while minimizing myelotoxicity. Trilaciclib (G1T28) is a highly potent and selective cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that causes a transient and reversible gap 1 (G_1) phase cell cycle arrest of hematopoietic stem and progenitor cells (HSPCs) within the bone marrow, thus protecting their deoxyribonucleic acid (DNA) from damage by chemotherapy and preserving long-term function. In nonclinical animal models, trilaciclib has been shown to induce a transient G_1 cell cycle arrest of the HSPCs and administration of trilaciclib prior to myelosuppressive chemotherapy resulted in improved recovery of complete blood counts (CBCs), preservation of the immune system numbers and function, maintenance of long-term bone marrow function, the ability to tolerate more cumulative chemotherapy, and the enhancement of chemotherapy antitumor efficacy. The retinoblastoma (RB) tumor suppressor gene is a critical negative cell cycle regulator that links growth factor signaling to cell cycle progression. When active, the retinoblastoma protein (Rb) blocks cell cycle progression by forming repressive complexes with transcription factors (notably the E2F family), which are critical for synthesis (S) phase entry and progression. CDK4 and CDK6 activate cell cycle progression primarily by phosphorylation and the subsequent suppression of RB. When RB is lost or inactivated, tumors cells become intrinsically resistant to CDK4/6 inhibition. Triple negative breast cancer (TNBC) exhibits frequent loss of RB through a variety of mechanisms, which leads to reduced Rb protein expression, high levels of p16ink4a (natural CDK4/6 inhibitor) expression, and very high expression levels of RB/E2F signature genes relative to other breast cancer subtypes. Additionally, the relationship between RB and development of TNBC is supported by the development of a breast

cancer mouse model in which conditional loss of p53 and RB leads to the development of breast cancer in the mice that exquisitely recapitulates human TNBC. Finally, gene expression analysis and immunohistochemical (IHC) approaches have shown that tumors that lack RB have a good response to chemotherapy, as indicated by a pathological complete response in neoadjuvant studies or improved overall outcome. This finding is counterintuitive because it suggests that the most aggressive rapidly growing tumors in fact have the best prognosis. The prevailing view of this paradox is that such rapidly proliferating tumors lack critical Rb-mediated cell cycle checkpoints and are thus very sensitive to chemotherapy. Since a RB-deficient phenotype is common in TNBC, it is expected that trilaciclib will have no effect on tumor growth or proliferation. Therefore, there is little concern that trilaciclib administered in combination with traditional chemotherapy (gemcitabine and carboplatin [GC]) will antagonize the intended efficacy of the chemotherapy. While trilaciclib is not expected to directly impact tumor proliferation, it has the potential to improve the current standard of care in TNBC by protecting the bone marrow and immune system during chemotherapy, thereby allowing faster hematopoietic recovery, preservation of long-term stem cell and immune system function, and enhancement of chemotherapy antitumor activity.

The dose of 240 mg/m^2 trilaciclib (established in 2 ongoing Phase 1b/2a small cell lung cancer [SCLC] studies) will be used for each administration of trilaciclib. However, 2 dosing schedules of trilaciclib will be tested. All 3 groups in the study will receive 21-day cycles of GC as the backbone chemotherapy. Patients in Group 1 will receive GC therapy on Days 1 and 8 with no trilaciclib. Patients in Group 2 will receive trilaciclib prior to GC therapy on Days 1 and 8. Patients in Group 3 will receive trilaciclib on Days 1, 2, 8, and 9, with administration prior to GC therapy on Days 2 and 9. The goals of this study are to assess the safety and tolerability of combining trilaciclib in 2 different schedules with GC therapy, to evaluate the effect of trilaciclib on chemotherapy-induced myelosuppression, and to evaluate the antitumor activity of trilaciclib + GC therapy (response rate, progression-free survival [PFS], and overall survival [OS]).

Clinical Phase	2
Indication	Reduction of chemotherapy-induced myelosuppression
Objectives	**Primary Objective**[a] Assess the safety and tolerability of trilaciclib administered with GC therapy **Secondary Objectives**[a] Assess tumor response and duration of response based on RECIST, Version 1.1 Assess PFS and OS Assess dose intensity of gemcitabine and carboplatin Assess the PK profile of trilaciclib Assess the PK profile of gemcitabine and carboplatin when administered with and without trilaciclib Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of trilaciclib administered with GC therapy Assess the incidence of febrile neutropenia Assess the incidence of infections Assess the utilization of RBC and platelet transfusions Assess the utilization of hematopoietic growth factors Assess the utilization of systemic antibiotics Assess the incidence of chemotherapy dose reductions and dose interruptions overall Assess the incidence of Grade 2 or greater nephrotoxicity Determine the dose schedule of trilaciclib administered with GC therapy CCI [redacted] GC therapy = gemcitabine + carboplatin on Days 1 and 8 or Days 2 and 9 of 21-day cycles; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; CCI [redacted]; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors a The objectives will be assessed for both schedules of trilaciclib (Days 1 and 8 or Days 1, 2, 8, and 9 in 21-day cycles) administered prior to GC therapy (Days 1 and 8 or Days 2 and 9 in 21-day cycles, respectively)

Study Design	This is a multicenter, randomized, open-label, Phase 2 study of the safety, efficacy, and pharmacokinetics (PK) of trilaciclib in combination with GC therapy for patients with metastatic TNBC. A total of approximately 90 patients will be randomly assigned (1:1:1 fashion) to 1 of the following 3 groups: • Group 1: GC therapy (Days 1 and 8 of 21-day cycles) only (n=30) • Group 2: GC therapy (Days 1 and 8) plus trilaciclib administered intravenous (IV) on Days 1 and 8 of 21-day cycles (n=30) • Group 3: GC therapy (Days 2 and 9) plus trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles (n=30) The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit. Randomization will be stratified as follows: liver involvement (yes or no) and the number of prior lines of anticancer therapy in the locally recurrent/metastatic setting at the time of randomization (0 or 1-2). **Criteria for Subsequent Cycles and Study Duration** In all 3 groups, study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons as described below. There should be no more than 4 weeks between doses of chemotherapy. Dosing delays > 4 weeks may be permitted on a case-by-case basis with the approval of the investigator and medical monitor. Patients must meet all of the following criteria to receive the Day 1/2 dose of each cycle: absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic toxicities must be ≤ Grade 2 or have returned to baseline. If the initiation of the next cycle is delayed due to toxicity, the patient should have (at least) weekly visits to follow the toxicity. Patients must meet all of the following criteria to receive the Day 8/9 dose of each cycle: ANC $\geq 1.0 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, and nonhematologic toxicities must be ≤ Grade 2 or have returned to baseline. If these criteria are not met, the Day 8/9 GC doses should be skipped; no dose reductions or delays are allowed for the Day 8/9 GC doses. If the Day 8/9 GC doses are skipped, the next GC doses become Day 1/2 of the subsequent cycle. There should be at least 7 days between a skipped Day 8/9 dose and the start of the next cycle, ie, Day 1/2. Note that the criteria for starting Day 1/2 outlined above will apply to resumption of dosing. The Survival Follow-up Phase of the study will continue until at least 50% of the patients on the study have died. The G1T28-04 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of

the study.

Safety Assessments

Safety assessments will include monitoring of adverse events (AEs) and infusion-related reactions, vital signs measurements, physical examinations, electrocardiograms (ECGs), and clinical laboratory studies. Tumor response criteria are based on RECIST, Version 1.1 (Eisenhauer et al. 2009), PFS, and OS.

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

Tumor Assessment

Tumor assessments will be based on RECIST v1.1. For tumor assessment, all sites of disease should be assessed radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) at screening and every 9 weeks ± 7 days (Week 9, Week 18, and Week 27) and then every 12 weeks ± 7 days thereafter until the occurrence of disease progression, withdrawal of consent, the initiation of subsequent anticancer therapy, or study completion. Tumor assessments should include CT with contrast or MRI with contrast (if clinically possible) of the chest and abdomen.

Radionuclide bone scans shall be performed at screening. Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan, should be imaged at baseline and followed at scheduled visits using localized CT, MRI, or x-ray. Bone scans need not be repeated after baseline unless clinically indicated.

Brain scans with contrast (by CT or MRI) shall be performed at screening for all patients. If brain metastases are present at screening, brain scans shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

Any CT, MRI, bone, or brain scan obtained as standard of care prior to screening will not need to be repeated if performed within the screening period.

Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. For those patients who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality as used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

Treatment Duration	Study drug administration will continue for each patient until disease progression per RECIST, Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first.
Study Duration	The total study duration is at least 19 months, assuming 12 months of accrual, 4 weeks of screening, 4.5 months of treatment (assuming 6 cycles), and 2 months of safety follow-up. The Survival Follow-up Phase will continue until at least 50% of the patients have died.
Approximate Number of Patients	Overall, approximately 90 patients will be enrolled in the study. The 90 patients will be randomly assigned (1:1:1) to 1 of 3 groups.
Number of Study Centers	Approximately 50 centers in North America and Europe
Diagnosis and Main Criteria for Inclusion	For a patient to be eligible for participation in this study, all of the following criteria must apply. 1. Female or male patients with evaluable locally recurrent or Stage IV metastatic TNBC 2. Age ≥ 18 years 3. Histologically or cytologically confirmed hormone (estrogen and progesterone) receptor negative tumor on local pathology IHC assessment (defined as < 10% nuclei staining) and human epidermal growth factor receptor 2 (HER2)-negative, nonoverexpressing (by local assessment of IHC [0 or 1+] OR fluorescent in situ hybridization [ratio < 2.0] OR average HER2 gene copy number of < 4 signals/nucleus) 4. Patients must have tumor tissue available from their TNBC diagnostic sample (archived tissue allowed) for retrospective analysis of potential biomarkers 5. Hemoglobin ≥ 9.0 g/dL in absence of RBC transfusion within 14 days prior to first dose of trilaciclib 6. ANC ≥ 1.5×10^9/L 7. Platelet count ≥ 100×10^9/L 8. Serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/minute 9. Total bilirubin ≤ 1.5 × upper limit of normal (ULN); < 3 × ULN if the patient has documented Gilbert's disease 10. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases 11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 12. Resolution of nonhematologic toxicities from prior therapy or surgical procedures to ≤ Grade 1 (except alopecia) 13. Predicted life expectancy of ≥ 3 months

14. Contraception:

a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and a negative serum or urine pregnancy test result at baseline (within 24 hours of the first dose). Females must be either postmenopausal, surgically sterile, or agree to use 2 forms of highly effective contraception during the study and for 6 months following discontinuation of study treatment

i. Postmenopausal is defined as at least 60 years of age, medically confirmed ovarian failure, younger than 60 years of age and have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause, and/or serum levels of estradiol and follicle stimulating hormone within the laboratory's reference range for postmenopausal females

ii. Acceptable surgical sterilization techniques are complete or partial hysterectomy or bilateral tubal ligation with surgery at least 6 months prior to dosing, and bilateral oophorectomy with surgery at least 2 months prior to dosing

iii. Highly effective methods of contraception are those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. These include the following:

1. Established use of oral, injected or implanted hormonal methods of contraception (stable dose at least 3 months prior to dosing)
2. Placement of an intrauterine device or intrauterine system
3. 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*
4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). *For female subjects on the study, the vasectomized male partner should be the sole partner for that subject*
5. True abstinence, when this is in line with the preferred and usual lifestyle of the subject. *Periodic abstinence (eg, calendar, ovulation,*

	symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception b. For males: Males must be surgically sterile or have a female partner who is either postmenopausal, surgically sterile, or using 2 forms of highly effective contraception as noted above. Acceptable surgical sterilization techniques are vasectomy with surgery at least 6 months prior to dosing. Males must also refrain from sperm donation during the study and for 6 months following discontinuation of treatment 15. Able to understand and sign an informed consent
Criteria for Exclusion	A patient will not be eligible for participation in this study if any of the following criteria apply. 1. More than 2 prior chemotherapy regimens for locally recurrent or metastatic TNBC (noncytotoxic therapies are not considered prior lines of therapy). For a regimen to be a line of therapy, the patient must have disease progression after that therapy prior to the start date of the next therapy or enrollment in this study. Therapy given in the neoadjuvant/adjuvant setting where the patient has recurrent disease > 12 months after the last dose of therapy will NOT be considered a line of therapy in the locally recurrent or metastatic setting. 2. Malignancies other than TNBC within 3 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome 3. Presence of CNS metastases/leptomeningeal disease requiring immediate treatment with radiation therapy or steroids (ie, patient must be off steroids administered for brain metastases for at least 14 days prior to the first dose of G1T28). 4. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (Class III or IV as defined by the New York Heart Association [NYHA] functional classification system) 5. Known history of stroke or cerebrovascular accident within 6 months prior to first dose of trilaciclib 6. Known serious active infection (eg, human immunodeficiency virus [HIV], hepatitis B or C, tuberculosis, etc.) 7. 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 8. Prior hematopoietic stem cell or bone marrow transplantation 9. Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to the first dose of trilaciclib

	10. Receipt of any investigational medication within 30 days prior to the first dose of trilaciclib 11. Receipt of any cytotoxic chemotherapy within 3 weeks prior to the first dose of trilaciclib 12. Receipt of any low-dose systemic chemotherapeutic agent given for a nononcologic purpose within 3 weeks prior to enrollment (eg, low-dose methotrexate for rheumatoid arthritis) 13. Hypersensitivity to cisplatin or other platinum-containing compounds, or mannitol 14. Pregnant or lactating women
Chemotherapy Treatment	Gemcitabine 1000 mg/m^2 and carboplatin area under the curve (AUC) = 2 administered IV on Days 1 and 8 (Groups 1 and 2) or on Days 2 and 9 (Group 3) of each 21-day cycle.
Investigational Medicinal Product Dosage and Administration	Trilaciclib 240 mg/m^2 in 250 mL of dextrose 5% in water (D5W) or in sodium chloride solution 0.9% administered as an IV infusion over 30 (± 5) minutes once daily on Days 1 and 8 (Group 2) or on Days 1, 2, 8, and 9 (Group 3) of each 21-day cycle.
Efficacy Evaluation	Trilaciclib efficacy evaluations will be based on the following: kinetics of changes in CBCs; hematologic toxicities, including febrile neutropenia and infections; RBC and platelet transfusions; hematopoietic growth factor utilization; systemic antibiotic use; chemotherapy dose reductions and dose interruptions; CCI ; CCI ; CCI ; CCI ; and CCI using the CCI instruments for breast cancer CCI and anemia CCI). Tumor response evaluations will be based on RECIST, Version 1.1, PFS, and OS.
Safety Evaluation	Safety will be assessed by evaluation of AEs, infusion-related reactions, physical examinations, vital sign measurements, ECGs, clinical laboratory data, and tumor response and duration of response based on RECIST, Version 1.1, PFS, and OS.
Pharmacokinetics Evaluation	Blood samples will be collected from a minimum of 6 patients enrolled in each treatment group for the measurement of trilaciclib, gemcitabine, and/or carboplatin concentrations in plasma. Participation in this part of the study is optional. <u>Cycle 1</u> Blood samples will be collected from a minimum of 6 patients in each treatment group on Cycle 1 Day 1 (Groups 1 and 2) or Cycle 1 Day 2 (Group 3). PK parameters (eg, maximum concentration [C_{max}], time to reach C_{max} [T_{max}], area under the concentration-time curve from time 0 to t [AUC_{0-t}], area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$], terminal half-life [$t_{1/2}$], volume of distribution in the terminal elimination phase [V_z], and clearance [CL]) will be derived from trilaciclib, gemcitabine, and carboplatin plasma concentration-time data.

CCI

[redacted]

Statistical Analysis	Data will be summarized descriptively by treatment group and for combined treatment Groups 2 and 3. Treatment differences between the GC therapy (Group 1) and each of the other treatment groups (Groups 2 and 3) will be estimated. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, and minimum and maximum values. The descriptive summaries of time-to-event data will include median, twenty-fifth and seventy-fifth percentiles, and standard error. All data will be listed for all patients. This study is descriptive in nature, and no formal hypothesis testing will be performed across treatment groups. All confidence intervals (CIs) will be 95%, unless stated otherwise. A DMC will perform interim reviews of accumulating safety and disposition data during the Treatment Phase. The final analysis will be performed after all patients have completed the Post-Treatment Visit. A supplemental analysis including the cumulative data collected during the Survival Follow-up Phase will be completed at the end of study. The full analysis set (FAS) includes all patients who received at least

	1 dose of study drug and will be the primary population for efficacy and exploratory endpoints. Summaries of efficacy will be performed using the FAS on hematologic kinetics, hematologic toxicity, infections, growth factor and antibiotic use, transfusions, chemotherapy exposure, and CCI . Select summaries will also be repeated in the per protocol (PP) analysis set. Unless noted otherwise, hematologic endpoints will be summarized separately by each parameter type (ie, ANC, lymphocytes, etc.). Analyses comparing treatment groups will adjust for prior chemotherapy regimens and other relevant parameters. Event rates will be calculated based on cumulative GC exposure to account for potential differences in GC exposure across treatment groups. The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. The incidence rates adjusted by cumulative exposure will also be presented overall and by cycle. Absolute values and changes from screening in vital signs, ECG readings, and hematology and clinical chemistry parameters will be tabulated at each visit during the Treatment Phase. Toxicities for clinical labs will be characterized according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Shifts in toxicity grades from screening to each visit will be summarized. Overall disease responses as determined by RECIST, Version 1.1, will be summarized by response level at each visit and best overall response. PFS and OS will be summarized using Kaplan-Meier methods. Plasma concentration-time data will be tabulated descriptively and plotted for each blood sampling day. PK parameters will be calculated using noncompartmental methods based on the plasma concentration-time data. PK parameters will be summarized descriptively by visit and analyte.
Rationale for Number of Patients	The sample size is not determined from a statistical perspective. Approximately 90 patients will be enrolled into the study (30 per treatment group).

4. INTRODUCTION

4.1. Background

Chemotherapy-induced myelosuppression is a significant issue in cancer treatment, including treatment of metastatic triple negative breast cancer (TNBC) (O'Shaughnessy et al. 2014). Patients with myelosuppression are more likely to experience infections, sepsis, bleeding, and fatigue, often leading to the need for hospitalizations, hematopoietic growth factor support, and transfusions (red blood cells [RBCs] and/or platelets). Moreover, chemotherapy-induced myelosuppression commonly leads to dose reductions which limit therapeutic dose intensity.

In addition to the side effects of chemotherapy, chemotherapy-induced immunosuppression may limit antitumor efficacy due to an inability of the host immune system to effectively mount a response against the cancer. Therefore, preserving the bone marrow and immune system from the cytotoxic effects of chemotherapy has the potential to maximize antitumor activity of the chemotherapy while minimizing myelotoxicity.

Targeted protection of the bone marrow and immune system through transient gap 1 (G_1) phase arrest of hematopoietic stem and progenitor cells (HSPCs) offers the potential to minimize myelotoxicity, while improving chemotherapy efficacy. This approach, previously described as "pharmacological quiescence," is built on several key principles: a highly potent cyclin-dependent kinase (CDK)4/6 inhibitor, highly selective for CDK4/6 versus CDK2 (and other kinases); the ability to harness cell cycle control with accuracy (ie, to produce a "clean" G_1 arrest, without inducing arrest in other phases of the cell cycle); and temporal precision (ie, the ability to regulate bone marrow proliferation as desired, producing a "transient, reversible" arrest) (Johnson et al. 2010; Roberts et al. 2012).

Trilaciclib (G1T28) is a highly potent, short-acting, selective, and reversible CDK4/6 inhibitor that transiently arrests cells in the G_1 phase of the cell cycle. Trilaciclib is being developed to preserve bone marrow and immune system function (including lymphoid progenitors and lymphocytes) from damage by chemotherapy, allowing faster hematopoietic recovery, preserving long-term bone marrow function, and enhancing the antitumor activity. In addition to preserving bone marrow function, trilaciclib administration prior to chemotherapy preserves lymphocyte numbers and function and transiently increases proliferation of lymphocytes and other immune cells coinciding with chemotherapy-associated neoantigen release. As a result of the effects on immune system function, trilaciclib could allow for maximal priming of the immune system to generate a more efficacious immune response.

The principal component of the therapeutic approach in this study is to transiently arrest HSPCs in the G_1 phase of the cell cycle while chemotherapy is administered. It is imperative that this therapeutic approach provides selective bone marrow protection without antagonizing the antitumor efficacy of chemotherapy. To ensure this second feature, patients are required to have CDK4/6-independent tumors. TNBC is a largely CDK4/6-independent tumor (Cancer Genome Atlas Network 2012; Gatza et al. 2014; Finn et al. 2009; Roberts et al. 2012; Treré et al. 2009). Therefore, trilaciclib administered prior to chemotherapy

(gemcitabine and carboplatin [GC]) in TNBC patients is unlikely to impact the intended activity of the chemotherapy agents.

4.2. Summary of Clinical Data

A brief summary of the clinical data is provided in the following sections. Detailed information is presented in the trilaciclib Investigator's Brochure (IB).

Study G1T28-1-01 was a Phase 1a, safety, pharmacokinetic (PK), and pharmacodynamic study of trilaciclib. Forty-five healthy male and female subjects were enrolled into 7 dose cohorts where trilaciclib was administered IV as a 30-minute infusion (randomized, double-blind, placebo-controlled ascending doses of 6, 12, 24, 48, 96, or 192 mg/m^2, and an open-label expanded pharmacodynamic cohort at 192 mg/m^2).

The most frequently (> 10% of subjects) reported adverse events (AEs) were the following: headache (17 subjects, 38%), nausea (10 subjects, 22%), pain in extremity (8 subjects, 18%), and procedural pain (7 subjects, 16%). The treatment-emergent AEs of headache and nausea occurred more frequently in the combined 192 mg/m^2 dose group (14 events of headache reported by 13 subjects [72%] and 10 events of nausea reported by 9 subjects [50%]) than in the lower dose groups. Most treatment-emergent AEs were mild in intensity; 13 subjects experienced a total of 19 treatment-emergent AEs of moderate intensity. Four AEs of moderate intensity occurred in the 96 mg/m^2 dose group (2 events of headache [possibly related], 1 event of back pain [unlikely related], and 1 event of nausea [possibly related]). Fifteen AEs of moderate intensity occurred in the combined 192 mg/m^2 dose group (7 events of headache [all possibly related], 6 events of nausea [all possibly related], 1 event of procedural anxiety [not related], and 1 event of loss of appetite [possibly related]). No severe or life-threatening events were reported. There were no deaths, other serious adverse events (SAEs), or treatment-emergent AEs resulting in withdrawal from the study. All treatment-emergent AEs were transient and recovered/resolved by the end of the study. No significant changes were noted in 12-lead electrocardiograms (ECGs), vital signs, or laboratory values (including complete blood counts [CBCs]).

Following a single 30-minute IV infusion of trilaciclib, the median time to reach the maximum concentration (T_{max}) ranged between 0.25 and 0.47 hour after the start of infusion. The maximum concentration (C_{max}) increased in a dose-proportional manner following a single 30-minute IV infusion of trilaciclib over the dose range of 6 to 192 mg/m^2. Total systemic (area under the concentration-time curve [AUC]) exposure increased more than dose proportionally over the dose range of 6 to 192 mg/m^2 of trilaciclib. The elimination kinetics of trilaciclib appeared to follow a 3-compartment model. The geometric mean half-life ($t_{1/2}$) was 12.9 to 14.7 hours for the 48 to 192 mg/m^2 dose levels. The interpatient variability (%CV) of the PK parameters at the 192 mg/m^2 dose level was low (< 15%). The PK of trilaciclib suggests that drug accumulation following repeated administration is unlikely to occur. Urinary excretion appears to be a minor route of elimination for unchanged trilaciclib.

Trilaciclib showed positive pharmacodynamic effects in 2 assays. Dose-dependent inhibition of ex vivo whole blood stimulation occurred following a single IV infusion of trilaciclib at 96 and 192 mg/m^2 (maximum mean inhibition of 37.2% and 60%, respectively, occurred

4 hours after the end of infusion). Lymphocyte proliferation started to recover 8 hours after the end of infusion, but inhibition of proliferation persisted until the last sampling time point of 24 hours. Assessment of bone marrow 24 hours after administration of trilaciclib at the biologically effective dose (BED) of 192 mg/m^2 revealed a significant decrease in the number of HSPCs in the synthesis (S)/gap 2 (G_2)/mitosis (M) phases of the cell cycle (ie, an increase in the proportion of cells in G_1 arrest). This G_1 arrest persisted in the different progenitor lineages 32 hours after dosing. However, no changes were noted in the peripheral blood counts, indicating that the bone marrow arrest is transient and reversible and is consistent with the effects seen in animals.

In 2 ongoing Phase 1b/2a studies (G1T28-02 and G1T28-03) in small cell lung cancer (SCLC), which is a CDK4/6-independent tumor, trilaciclib administered prior to every dose of etoposide and carboplatin (first line for extensive-stage SCLC) and prior to every dose of topotecan (second/third line for SCLC) are being tested. Early results have demonstrated minimal clinically significant myelotoxicity at the recommended Phase 2 dose of trilaciclib (240 mg/m^2) when administered prior to chemotherapy, and antitumor activity has been consistent with or better than historical data.

In G1T28-02, as of the data cutoff date of 20-May-2016, the majority of patients (81.8%; 9 of 11) reported TEAEs, with the most common (ie, reported by > 30% of patients) being fatigue, nausea, anemia, neutropenia, and alopecia. TEAEs considered related to trilaciclib per investigator assessment were reported by 4 patients (36.4%). The majority of patients (72.7%) reported at least 1 Grade 3, 4, or 5 TEAE; those reported by more than 1 patient included neutropenia, anemia, leukopenia, and lymphopenia. Less than one-half of patients (36.4%) reported an SAE; all of which were considered unlikely or not related to trilaciclib and did not meet dose-limiting toxicity (DLT) criteria. One patient died during participation in the study due to an SAE of hypoxia that was considered unrelated to trilaciclib by the investigator.

In G1T28-03, as of the data cutoff date of 20-May-2016, the majority of patients (92.9%; 13 of 14) reported TEAEs, with the most common (ie, reported by > 50% of patients) being thrombocytopenia, neutropenia, anemia, and leukopenia. TEAEs considered related to trilaciclib per investigator assessment were reported by 4 patients (28.6%). The majority of patients (85.7%) reported at least 1 Grade 3, 4, or 5 TEAE; those reported by more than 1 patient included thrombocytopenia, leukopenia, neutropenia, anemia, neutrophil count decreased, pneumonia, and dyspnea. The majority of the Grade 3, 4, or 5 TEAEs have been reported by patients in Cohorts 1 and 2, likely due to the supratherapeutic levels of topotecan observed in these patients, which may be responsible for the higher number of hematology-related TEAEs in Cohorts 1 and 2. Over one-half of patients (64.3%) reported an SAE, all of which were considered unlikely or not related to trilaciclib and did not meet DLT criteria. One patient died during participation in the study due to an SAE of disease progression that was considered unrelated to trilaciclib by the investigator.

The PK assessments of trilaciclib in the ongoing studies support the findings from the study in healthy male and female subjects (GT128-01). Clearance was observed to be high, with little or no drug accumulation during 3 or 4 days of dosing, except at the trilaciclib 280 mg/m^2 dose level tested in Study G1T28-03.

CCI

[redacted]

4.3.1. 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 [IC_{50}] values of 0.8 and 6 nM, respectively) that is highly selective for CDK4 versus cyclin-dependent kinase 2 (CDK2) (> 2000-fold selectivity).

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 in combination with myelosuppressive chemotherapy leads to improved CBC recovery of all blood lineages and increased survival. In addition, administration of trilaciclib with every cycle of the highly myelosuppressive chemotherapy 5-fluorouracil (5-FU) for a total of 4 cycles demonstrated that the reduction in chemotherapy-induced myelosuppression persisted following Cycle 4. While the extent and duration of nadir in CBCs worsened after each cycle of 5-FU administered alone, trilaciclib in combination with 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. In accordance with the single-dose study, trilaciclib administration with all cycles of 5-FU maintained the protective effect against 5-FU-induced DNA damage in HSPCs over multiple cycles, leading to an effect that persisted and was greater following multiple cycles of trilaciclib + 5-FU compared with 5-FU alone.

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[redacted]

The retinoblastoma (RB) tumor suppressor gene is a critical negative cell cycle regulator that links growth factor signaling to cell cycle progression. Signaling pathways that stimulate proliferation impinge on the cell cycle machinery in several ways including the augmenting production of D-type cyclins. Accumulation of D-type cyclins along with concomitant activation of their catalytic partners, CDK4 and CDK6, has been shown to activate cell cycle progression primarily by phosphorylation and the subsequent suppression of RB. When active, the retinoblastoma protein (Rb) locks cell cycle progression by forming repressive complexes with transcription factors (notably the E2F family), which are critical for S phase entry and progression. Unlike human epidermal growth factor receptor 2 (HER2)-positive or estrogen receptor (ER)-positive breast cancers that have relatively limited loss of RB, TNBC exhibits frequent loss of RB through a variety of mechanisms (Treré et al. 2009; Herschkowitz et al. 2008; Stefansson et al. 2011), which leads to reduced Rb protein expression, high levels of p16ink4a observed in many TNBC cases (Subhawong et al. 2009), and very high expression levels of RB/E2F signature genes relative to other tumor subtypes (Herschkowitz et al. 2008; Ertel et al. 2010). Additionally, the relationship between RB and development of TNBC is supported by the development of a breast cancer mouse model in which conditional loss of p53 and RB leads to the development of breast cancer in the mice that exquisitely recapitulates human TNBC (Maroulakou et al. 1994). Finally, gene expression analysis and immunohistochemical (IHC) approaches have shown that tumors that lack RB have a good response to chemotherapy, as indicated by a pathological complete response in neoadjuvant studies or improved overall outcome (Herschkowitz et al. 2008; Ertel et al. 2010; Witkiewicz et al. 2012). This finding is counterintuitive because it suggests that the most aggressive rapidly growing tumors in fact have the best prognosis. The prevailing view of this paradox is that such rapidly proliferating tumors lack critical Rb-mediated cell cycle checkpoints and are thus very sensitive to chemotherapy (Knudsen & Wang 2010; Robinson et al. 2013). Since a RB-deficient phenotype is common in TNBC, it is expected that trilaciclib will have no effect on tumor growth or proliferation. Therefore, there is little concern that trilaciclib administered in combination with traditional chemotherapy (GC) will antagonize the intended efficacy of the chemotherapy. While trilaciclib is not expected to directly impact tumor proliferation, it has the potential to greatly improve the current standard of care in TNBC by protecting the bone marrow and immune system during chemotherapy, thereby allowing faster hematopoietic recovery, preservation of long-term stem cell and immune system function, and enhancement of chemotherapy antitumor activity.

CCI

Gemcitabine has not been reported to be a substrate for MATE1 or MATE2 (Blackhall et al. 2010; Shen et al. 2013), and is not believed to be a substrate for OCT2. As such, a clinically significant alteration of gemcitabine PK due to trilaciclib transporter (OCT2, MATE1, or MATE2-K) inhibition is not expected.

Carboplatin has not been reported to be a substrate for OCT2, MATE1, or MATE2 (Yonezawa 2006). Based upon these data, a clinically significant alteration of carboplatin PK due to trilaciclib inhibition of OCT2, MATE1, or MATE2-K is not expected.

4.3.3. Toxicity and Safety Studies

The toxicity of IV and oral trilaciclib was evaluated in single- and repeat-dose studies of up to 14 days duration in rats and dogs and in a battery of in vitro genotoxicity studies. In addition, the compatibility of trilaciclib clinical drug product with human blood was evaluated in vitro.

For further information, please refer to the trilaciclib IB.

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Although trilaciclib induced micronucleus formation in human lymphocytes exposed in vitro, trilaciclib is not considered to pose a hazard to human patients, as trilaciclib was negative for mutagenic potential in a Good Laboratory Practice (GLP) (and non-GLP) Ames assay, and did not induce phosphorylated histone H2AX (γH2AX) formation in primary human fibroblasts. In the present study, trilaciclib will be administered in conjunction with GC, which presents a genotoxic hazard to human subjects. In this context, any slight additional genotoxic hazard posed by trilaciclib is negligible.

CCI

4.4. Study and Dose Rationale

Triple negative breast cancer has been characterized by several aggressive clinicopathologic features including onset at a younger age, higher mean tumor size, higher grade tumors, and, in some cases, a higher rate of node positivity. Population-based studies have demonstrated reduced breast cancer-specific survival among patients with TNBC compared with receptor positive phenotypes. While targeted-based therapies have greatly impacted other subtypes of breast cancer, no targeted-based approaches have been approved for TNBC patients. Therefore, this group of patients continues to rely on the use of traditional cytotoxic agents. Interestingly, a paradox of higher sensitivity to neoadjuvant anthracycline therapy has been observed in patients with TNBC, who as stated above are known to have a poor prognosis (Liedtke et al. 2008; Carey et al. 2007; Rouzier et al. 2005). This observation is explained by the fact that women with TNBC who achieve a pathological complete response have similar outcomes as other breast cancer patients. However, women with the basal-like subtype that do not achieve a complete response have a significantly higher rate of recurrence and lower rate of survival. This finding highlights the importance of delivering full dose and scheduled chemotherapy in the treatment of basal-like breast cancer to ensure maximal response. However, chemotherapeutic regimens are often limited by toxic side effects that require reductions in chemotherapy dose intensity, through dose reductions, treatment delays, or stopping treatment all together. Myelosuppression is the major DLT of cancer chemotherapy, resulting in considerable morbidity and mortality along with frequent reductions in chemotherapy dose intensity. Reductions in chemotherapy dose intensity have been repeatedly shown to compromise disease control and survival of cancer patients including patients with TNBC.

The goals of this study are to assess the safety and tolerability of combining trilaciclib in 2 different schedules with GC therapy, to evaluate the effect of trilaciclib on chemotherapy-induced myelosuppression, and to evaluate the antitumor activity of trilaciclib + GC therapy (response rate, duration of response, progression-free survival [PFS], and overall survival [OS]). Group 3 of the study will test if there is added benefit in achieving maximal arrest of the bone marrow stem and progenitors prior to chemotherapy administration. In naïve bone marrow of humans and other species, the majority of the hematopoietic stem cells and multipotent progenitor cells are arrested in the G_1 phase of the cell cycle. However, proliferation of these cells greatly increases upon exposure to cytotoxic chemotherapy, making them more susceptible to chemotherapy exposure on subsequent days. In nonclinical animal studies, trilaciclib administration begins to arrest cells in the G_1 phase of the cell cycle within 2 hours after administration and produces maximal arrest between 8 to 12 hours. In humans, a single dose of trilaciclib has been shown to maintain G_1 arrest for at least 32 hours. Previous clinical studies testing trilaciclib in combination with chemotherapy have used regimens where the chemotherapy was administered in consecutive days (1-3 or 1-5 of 21-day cycles). In these scenarios, it is believed that continued G_1 arrest throughout the period of chemotherapy administration is required to prevent the compensatory proliferative increase of the HSPCs and their subsequent damage while chemotherapy is being administered on days 2 and beyond. In this study, the chemotherapy is not given on consecutive days, so it is reasonable to test if a predose of trilaciclib administered the day before and the day of chemotherapy would add additional benefit by producing maximal HSPC G_1 arrest at the time of chemotherapy administration. Additionally, it is unknown if HSPC proliferation will be increased on Day 8/9 of dosing

compared to baseline. If so, a dose of trilaciclib the day before may provide additional benefit by reducing HSPC proliferation prior to chemotherapy administration on Day 9.

4.5. Risk/Benefit Assessment

Trilaciclib (CDK 4/6 inhibitor) is being developed to reduce chemotherapy-induced myelosuppression, which is known to cause morbidity and mortality in cancer patients. Patients with myelosuppression are more likely to experience infections, sepsis, bleeding, and fatigue, often leading to the need for hospitalizations, hematopoietic growth factor support, and transfusions (RBCs and/or platelets). Moreover, chemotherapy-induced myelosuppression commonly leads to dose reductions which limit therapeutic dose intensity. In addition to the side effects of chemotherapy, chemotherapy-induced immunosuppression may limit antitumor 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 immune system from the cytotoxic effects of chemotherapy has the potential to maximize antitumor activity of the chemotherapy while minimizing myelotoxicity. As stated in Section 4.2, the dose of 240 mg/m^2 trilaciclib established in Phase 1b/2a SCLC studies will be administered in combination with a commonly used chemotherapy regimen of GC in order to determine if this will help preserve bone marrow and immune system function during chemotherapy. Bone marrow HSPCs require CDK4/6 for proliferation. Triple negative breast cancer is a largely CDK4/6-independent tumor (Cancer Genome Atlas Network 2012; Gatza 2014; Finn 2009; Roberts 2012; Treré 2009). Therefore, the risk of producing a G_1 cell cycle arrest of the tumor cells, and thereby protecting the tumor from chemotherapy, is small.

In conclusion, there are potential benefits of combining trilaciclib at a dose of 240 mg/m^2 with GC therapy to protect the bone marrow HSPCs. Given that the tumor response should not be inhibited by trilaciclib, the potential benefit of combining GC with trilaciclib creates a positive benefit-to-risk ratio.

5. STUDY OBJECTIVES

The primary, secondary, and CCI objectives of this study are presented in Table 5-1.

Table 5-1 G1T28-04: Study Objectives

Primary Objective[a]
Assess the safety and tolerability of trilaciclib administered with GC therapy
Secondary Objectives[a]
Assess tumor response and duration of response based on RECIST, Version 1.1
Assess PFS and OS
Assess dose intensity of gemcitabine and carboplatin
Assess the PK profile of trilaciclib
Assess the PK profile of gemcitabine and carboplatin when administered with and without trilaciclib
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of trilaciclib administered with GC therapy
Assess the incidence of febrile neutropenia
Assess the incidence of infections
Assess the utilization of RBC and platelet transfusions
Assess the utilization of hematopoietic growth factors
Assess the utilization of systemic antibiotics
Assess the incidence of chemotherapy dose reductions and dose interruptions overall
Assess the incidence of Grade 2 or greater nephrotoxicity
Determine the dose schedule of trilaciclib administered with GC therapy
CCI

GC therapy = gemcitabine + carboplatin on Days 1 and 8 or Days 2 and 9 of 21-day cycles; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; CCI; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

a. The objectives will be assessed for both schedules of trilaciclib (Days 1 and 8 or Days 1, 2, 8, and 9 in 21-day cycles) administered prior to GC therapy (Days 1 and 8 or Days 2 and 9 in 21-day cycles, respectively)

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This is a multicenter, randomized, open-label, Phase 2 study of the safety, efficacy, and PK of trilaciclib in combination with GC therapy for patients with metastatic TNBC. A total of approximately 90 patients will be randomly assigned (1:1:1 fashion) to 1 of the following 3 groups:

- Group 1: GC therapy (Days 1 and 8 of 21-day cycles) only (n=30)
- Group 2: GC therapy (Days 1 and 8) plus trilaciclib administered IV on Days 1 and 8 of 21-day cycles (n=30)
- Group 3: GC therapy (Days 2 and 9) plus trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles (n=30)
  Note: The interval between doses of trilaciclib on successive days in Group 3 should not be greater than 28 hours. Trilaciclib will be administered 30 minutes prior to GC dosing on Days 2 and 9.

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit.

7. STUDY POPULATION

7.1. Selection of Patients

Overall, approximately 90 patients will be enrolled in the study. The 90 patients will be randomly assigned (1:1:1) to 1 of 3 groups.

The study will be conducted at approximately 50 centers in North America and Europe.

7.1.1. Inclusion Criteria

For a patient to be eligible for participation in this study, *all* of the following criteria must apply.

1. Female or male patients with evaluable locally recurrent or Stage IV metastatic TNBC
2. Age ≥ 18 years
3. Histologically or cytologically confirmed hormone (estrogen and progesterone) receptor negative tumor on local pathology IHC assessment (defined as < 10% nuclei staining) and HER2-negative, nonoverexpressing (by local assessment of IHC [0 or 1+] OR fluorescent in situ hybridization [ratio < 2.0] OR average HER2 gene copy number of <4 signals/nucleus)
4. Patients must have tumor tissue available from their TNBC diagnostic sample (archived tissue allowed) for retrospective analysis of potential biomarkers
5. Hemoglobin ≥ 9.0 g/dL in absence of RBC transfusion within 14 days prior to first dose of trilaciclib
6. ANC ≥ 1.5×10^9/L
7. Platelet count ≥ 100×10^9/L
8. Serum creatinine of ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/minute
9. Total bilirubin ≤ 1.5 × upper limit of normal (ULN); < 3 × ULN if the patient has documented Gilbert's disease
10. AST and ALT ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
12. Resolution of nonhematologic toxicities from prior therapy or surgical procedures to ≤ Grade 1 (except alopecia)
13. Predicted life expectancy of ≥ 3 months
14. Contraception:

a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and a negative serum or urine pregnancy test result at baseline (within 24 hours of the first dose). Females must be either postmenopausal, surgically sterile, or agree to use 2 forms of highly effective contraception during the study and for 6 months following discontinuation of study treatment

   i. Postmenopausal is defined as at least 60 years of age, medically confirmed ovarian failure, younger than 60 years of age and have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause, and/or serum levels estradiol and of follicle stimulating hormone within the laboratory's reference range for postmenopausal females

   ii. Acceptable surgical sterilization techniques are complete or partial hysterectomy or bilateral tubal ligation with surgery at least 6 months prior to dosing, and bilateral oophorectomy with surgery at least 2 months prior to dosing

   iii. Highly effective methods of contraception are those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. These include the following:

      1. Established use of oral, injected or implanted hormonal methods of contraception (stable dose at least 3 months prior to dosing)
      2. Placement of an intrauterine device or intrauterine system
      3. 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*
      4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). *For female subjects on the study, the vasectomized male partner should be the sole partner for that subject*
      5. True abstinence, when this is in line with the preferred and usual lifestyle of the subject. *Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception*

b. For males: Males must be surgically sterile or have a female partner who is either postmenopausal, surgically sterile, or using 2 forms of highly effective contraception as noted above. Acceptable surgical sterilization techniques are vasectomy with surgery at least 6 months prior to dosing. Males must also refrain from sperm donation during the study and for 6 months following discontinuation of treatment

15. Able to understand and sign an informed consent

7.1.2. Exclusion Criteria

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

1. More than 2 prior chemotherapy regimens for locally recurrent or metastatic TNBC (non-cytotoxic therapies are not considered prior lines of therapy). For a regimen to be a line of therapy, the patient must have disease progression after that therapy prior to the start date of the next therapy or enrollment in this study. Therapy given in the neoadjuvant/adjuvant setting where the patient has recurrent disease > 12 months after the last dose of therapy will NOT be considered a line of therapy in the locally recurrent or metastatic setting.
2. Malignancies other than TNBC within 3 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome
3. Presence of CNS metastases/leptomeningeal disease requiring immediate treatment with radiation therapy or steroids (ie, patient must be off steroids administered for brain metastases for at least 14 days prior to the first dose of G1T28).
4. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (Class III or IV as defined by the New York Heart Association [NYHA] functional classification system)
5. Known history of stroke or cerebrovascular accident within 6 months prior to first dose of trilaciclib
6. Known serious active infection (eg, human immunodeficiency virus [HIV], hepatitis B or C, tuberculosis, etc.)
7. 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
8. Prior hematopoietic stem cell or bone marrow transplantation
9. Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to the first dose of trilaciclib
10. Receipt of any investigational medication within 30 days prior to the first dose of trilaciclib
11. Receipt of any cytotoxic chemotherapy within 3 weeks prior to the first dose of trilaciclib
12. Receipt of any low-dose systemic chemotherapeutic agent given for a nononcologic purpose within 3 weeks prior to enrollment (eg, low-dose methotrexate for rheumatoid arthritis)
13. Hypersensitivity to cisplatin or other platinum-containing compounds, or mannitol
14. Pregnant or lactating women

8. TREATMENTS

8.1. Treatments Administered

Patients will be randomly assigned (1:1:1 fashion) to receive 1 of the following 3 treatments:

- Group 1: GC therapy (Days 1 and 8 of 21-day cycles) only
- Group 2: GC therapy (Days 1 and 8) plus trilaciclib administered IV on Days 1 and 8 of 21-day cycles
- Group 3: GC therapy (Days 2 and 9) plus trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles

In Groups 1 and 2, patients will receive GC chemotherapy (gemcitabine 1000 mg/m^2 and carboplatin AUC = 2 administered IV) on Days 1 and 8 in 21-day cycles. In Group 3, patients will receive GC chemotherapy on Days 2 and 9 in 21-day cycles. The carboplatin dose will be calculated using the Calvert formula with a target AUC = 2 (maximum 300 mg) IV.

In Groups 2 and 3, trilaciclib (240 mg/m^2) will be administered as an IV infusion over 30 (± 5) minutes prior to each GC treatment (on Days 1 and 8 for Group 2 and on Days 2 and 9 for Group 3). In Group 3, trilaciclib (240 mg/m^2) will also be administered on Days 1 and 8. The interval between doses of trilaciclib on successive days in Group 3 should not be greater than 28 hours.

Study drug administration will continue until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities (see Section 8.4.3).

8.2. Investigational Products

8.2.1. Identity

8.2.1.1. Trilaciclib

Trilaciclib is supplied as a single-use, sterile powder with 300 mg trilaciclib in each 30-mL flint glass vial. CCI, USP is added as a cake forming agent and CCI buffer is added to maintain the reconstituted pH at 4.0 to 5.0. The process for reconstitution of study drug is detailed in the Pharmacy Manual.

8.2.1.2. Gemcitabine and Carboplatin

Descriptions of the formulations of commercially-available gemcitabine and carboplatin can be found in the respective current prescribing information (see Appendix 2).

8.2.2. Packaging and Labeling

8.2.2.1. Trilaciclib

Trilaciclib sterile powder is manufactured and packaged by PPD

Individual vials of trilaciclib will be labeled and supplied to the pharmacist/designee who will inventory the contents and document them according to the drug accountability requirements (Section 8.2.5).

8.2.2.2. Gemcitabine and Carboplatin

Descriptions of the packaging and labeling of commercially-available gemcitabine and carboplatin can be found in the respective current prescribing information (see Appendix 2).

8.2.3. Storage

8.2.3.1. Trilaciclib

The trilaciclib sterile powder 300 mg/30 mL vial should be stored under refrigerated conditions at CCI .

Stability data for the current formulation of trilaciclib sterile powder formulation demonstrates satisfactory stability for up to CCI at CCI and for up to CCI at CCI . Based on these stability data, we are allowing shipment of trilaciclib under ambient conditions. Once the drug has arrived at site, it should be refrigerated.

Study drugs will be stored in a CCI in a secured room and only the pharmacist/designee and designated personnel will have access to the study drugs.

8.2.3.2. Gemcitabine and Carboplatin

Information regarding the storage of commercially-available gemcitabine and carboplatin can be found in the respective current prescribing information (see Appendix 2).

8.2.4. Procedure for Dispensing

Dispensing instructions will be provided in the Pharmacy Manual and will be maintained in the pharmacy records.

8.2.5. Investigational Product Accountability

The pharmacist/designee will verify the integrity of the clinical trial supplies (storage conditions, correct amount received, condition of shipment, vial numbers, etc.) according to the investigative site's standard operating procedures (SOPs).

At a minimum, the following data will be tracked on the drug accountability log at the site pharmacy:

- Date received
- Lot number
- Vial number
- Date dispensed
- Patient number
- Identification of the person dispensing the drug

Records of study medication (used, lost, destroyed, and returned containers, individual vials) should be made at each visit in the drug accountability and dispensing forms. Drug accountability and reconciliation will be checked and verified by the pharmacy team during the study and by the site monitor during and at the completion of the study.

Once the site monitor has verified drug accountability at the site, any used drug remaining at the completion of the study will be destroyed. Unused and unopened study medication will be returned by the site monitor to the sponsor or may be destroyed on site according to the investigative site's SOPs.

8.3. Method of Assigning Patients to Treatment Groups

A unique patient identification number will be assigned to each patient who signs an informed consent form.

Patients meeting all inclusion and exclusion criteria will be randomized 1:1:1 to receive study drug as described in Section 8.1. Each patient will be assigned a unique identification number, which will not be reused.

8.4. Dose, Dosing Regimen, and Route

For trilaciclib or gemcitabine dosing, the body surface area (BSA) calculation should use the actual body weight, not the ideal body weight. If a patient's weight fluctuates from visit to visit, the dose of trilaciclib or gemcitabine can be adjusted at each visit OR the dose need not be adjusted unless the change in actual body weight is $\geq$ 10%.

8.4.1. Trilaciclib

Trilaciclib (240 mg/m^2) diluted in 250 mL of [redacted] in [redacted] is to be administered by IV infusion over 30 ±5 minutes. If there is any study drug remaining in the infusion bag at the end of the 30 ±5 minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. The infusion rate may be decreased to manage an infusion-related AE; for example, if a patient experiences a burning sensation during infusion, the infusion time may be increased to 45 minutes (or longer if clinically indicated) to alleviate the symptoms. The actual time of infusion will be documented and entered in the electronic case report form (eCRF). Details regarding the reconstitution and dilution of trilaciclib vials are detailed in the Pharmacy Manual.

On chemotherapy dosing days, trilaciclib is always administered first. The interval between doses of trilaciclib on successive days in Group 3 should not be greater than 28 hours. If administration of GC therapy is discontinued, trilaciclib will also be discontinued.

8.4.2. Gemcitabine and Carboplatin

Gemcitabine and carboplatin will be administered IV in accordance with the instructions below.

Needles or IV administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

On chemotherapy dosing days, trilaciclib is always administered first, followed by GC. GC 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 chemotherapy (gemcitabine or carboplatin) administration should not be greater than 4 hours.

If administration of trilaciclib is discontinued, GC therapy will also be discontinued.

8.4.2.1. Carboplatin

The carboplatin dose will be calculated using the Calvert formula with a target AUC = 2 on Days 1 and 8 (Groups 1 and 2) or Days 2 and 9 (Group 3) of each 21-day cycle and administered as an IV infusion according to the local package insert.

The Calvert formula is as follows:

Total carboplatin dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25)

Because each patient's estimated GFR will be based on serum creatinine measurements, the **dose of carboplatin should be capped at 300 mg** to avoid potential toxicity due to overdosing. The cap dose of 300 mg for carboplatin is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function (ie, maximum carboplatin dose = target AUC of 2 mg•min/mL × 150 = 300 mg).

8.4.2.2. Gemcitabine

Gemcitabine 1000 mg/m^2 will be administered as an IV infusion according to the local package insert on Days 1 and 8 (Groups 1 and 2) or Days 2 and 9 (Group 3) of each 21-day cycle.

8.4.3. Toxicity Management Guidelines

The dose of trilaciclib will not be modified and will remain at 240 mg/m^2 throughout the study. If administration of GC therapy is discontinued, trilaciclib will also be discontinued.

Gemcitabine and carboplatin dose reductions are permitted according to the organ system showing the greatest degree of drug-related toxicity. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

8.4.3.1. Criteria for Subsequent Cycles

In all 3 groups, study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator.

There should be no more than 4 weeks between doses of chemotherapy in all groups. Dosing delays greater than 4 weeks may be permitted on a case by case basis with the approval of the investigator and medical monitor.

Criteria for Day 1/2 of Each Cycle

Patients must meet all of the following criteria to receive the Day 1/2 dose:

- ANC $\geq 1.0 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Nonhematologic toxicities (except alopecia) must be $\leq$ Grade 2 or have returned to baseline

If the initiation of the next cycle is delayed due to toxicity, the patient should have (at least) weekly visits to follow the toxicity. Delayed dosing visits will be captured in the eCRF.

Criteria for Day 8/9 of Each Cycle

To receive Day 8/9 dose of each cycle, patients must meet all the following criteria:

- ANC $\geq 1.0 \times 10^9$/L
- Platelet count $\geq 75 \times 10^9$/L
- Nonhematologic toxicities (except alopecia) must be $\leq$ Grade 2 or have returned to baseline

If these criteria are not met, the Day 8/9 GC doses should be skipped; no dose reductions or delays are allowed for the Day 8/9 GC doses. If the Day 8/9 GC doses are skipped, the next GC doses become Day 1/2 of the subsequent cycle. There should be at least 7 days between a skipped Day 8/9 dose and the start of the next cycle, ie, Day 1/2. Note that the criteria for starting Day 1/2 outlined above will now apply to resumption of dosing.

8.4.3.2. Dose Modifications for Hematologic Toxicity

Section 8.4.3.1 outlines the hematologic criteria each patient must meet to receive study drug(s) on Day 1/2 and Day 8/9 of each cycle. Dose reductions for hematologic toxicities are based on values obtained within 24 hours of chemotherapy and all dose reductions will only be made on Day 1/2 of a cycle (Table 8-1). All dose reductions are permanent and no dose increases will occur following a dose reduction. Day 8/9 GC treatment will either be

administered at the same dose levels as the Day 1/2 GC doses of that cycle or will be skipped. There will be no Day 8/9 GC dose reductions.

Table 8-1 Dose Modification for Hematologic Toxicity (All Groups)

		Action Taken			
Grade (Gr) or Lab Value	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
ANC value on scheduled Day 1/2 in Cycle 2 and any subsequent cycle or when previous Day 8/9 skipped					
ANC < 1.0×10^9/L **OR** Previous cycle Day 8/9 skipped due to ANC < 1.0×10^9/L	First episode	Hold drug until ANC criteria for dosing reached; no change in dose	Hold drug until ANC criteria for dosing reached; no change in dose	Hold drug until ANC criteria for dosing reached; no change in dose	Administer G-CSF with each subsequent cycle after chemotherapy
	Second episode	Hold drug until ANC criteria for dosing reached; reduce to 800 mg/m^2	Hold drug until ANC criteria for dosing reached; no change in dose	Hold drug until ANC criteria for dosing reached; no change in dose	Continue G-CSF with each subsequent cycle after chemotherapy
	Third episode	Hold drug until ANC criteria for dosing reached; continue 800 mg/m^2	Hold drug until ANC criteria for dosing reached; reduce to AUC 1.5	Hold drug until ANC criteria for dosing reached; no change in dose	Continue G-CSF with each subsequent cycle after chemotherapy
	Fourth episode	Hold drug until ANC criteria for dosing reached; permanently discontinue either gemcitabine or carboplatin and continue the other drug at the reduced dose		Hold drug until ANC criteria for dosing reached; no change in dose	Continue G-CSF with each subsequent cycle after chemotherapy
	Fifth episode	Permanently discontinue all study drugs		Permanently discontinue	

		Action Taken			
Grade (Gr) or Lab Value	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
Platelet value on Day 1/2 in Cycle 2 and any subsequent cycle or when previous Day 8/9 skipped					
Platelets < 100×10^9/L **OR** Previous Day 8/9 platelets < 75×10^9/L	First episode	Hold drug until platelet criteria for dosing reached; reduce to 800 mg/m^2	Hold drug until platelet criteria for dosing reached; no change in dose	Hold drug until platelet criteria for dosing reached; no change in dose	Monitor for signs/symptoms of bleeding.
	Second episode	Hold drug until platelet criteria for dosing reached; continue 800 mg/m^2	Hold drug until platelet criteria for dosing reached; reduce to AUC 1.5	Hold drug until platelet criteria for dosing reached; no change in dose	
	Third episode	Hold drug until platelet criteria for dosing reached; permanently discontinue either gemcitabine or carboplatin and continue the other drug at the reduced dose		Hold drug until platelet criteria for dosing reached; no change in dose	
	Fourth episode	Permanently discontinue all study drugs		Permanently discontinue	
ANC and/or platelet values on scheduled Day 8/9 in Cycle 2 and any subsequent cycle					
ANC < 1.0×10^9/L **AND/OR** platelets < 75×10^9/L	Any event	Skip dose	Skip dose	Skip dose	Administer G-CSF with each subsequent cycle after chemotherapy if the ANC criteria is met

		Action Taken			
Grade (Gr) or Lab Value	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
Febrile neutropenia per CTCAE v 4.03 at any point during the study					
Febrile neutropenia	First episode	Hold drug until ANC criteria for dosing reached; no change in dose	Hold drug until ANC criteria for dosing reached; no change in dose	Hold drug until ANC criteria for dosing reached; no change in dose	Administer G-CSF with each subsequent cycle after chemotherapy
	Second episode	Hold drug until ANC criteria for dosing reached; reduce to 800 mg/m^2	Hold drug until ANC criteria for dosing reached; no change in dose	Hold drug until ANC criteria for dosing reached; no change in dose	Continue G-CSF with each subsequent cycle after chemotherapy
	Third episode	Hold drug until ANC criteria for dosing reached; continue 800 mg/m^2	Hold drug until ANC criteria for dosing reached; reduce to AUC 1.5	Hold drug until ANC criteria for dosing reached; no change in dose	Continue G-CSF with each subsequent cycle after chemotherapy
	Fourth episode	Permanently discontinue	Permanently discontinue	Permanently discontinue	
Symptomatic thrombocytopenia at any point in the study					
≥ Gr 3 with bleeding	First episode	Hold drug until platelet criteria for dosing reached; reduce to 800 mg/m^2	Hold drug until platelet criteria for dosing reached; no change in dose	Hold drug until platelet criteria for dosing reached; no change in dose	
	Second episode	Hold drug until platelet criteria for dosing reached; continue 800 mg/m^2	Hold drug until platelet criteria for dosing reached; reduce to AUC 1.5	Hold drug until platelet criteria for dosing reached; no change in dose	
	Third episode	Permanently discontinue	Permanently discontinue	Permanently discontinue	

8.4.3.3. Use of Colony Stimulating Factors

Use of **prophylactic** colony stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF]; granulocyte-macrophage colony-stimulating factor [GM-CSF]) **during Cycle 1** (ie, 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 Tables 8-1, which are based on the ASCO guidelines for neutropenia (Smith 2015) and package inserts (see Appendix 3). Short-acting G-CSF products (ie, Neupogen or biosimilars) may be administered starting 24 to 48 hours after the dose of chemotherapy on Day 1/2 or Day 8/9 and must be stopped 48 hours prior to trilaciclib administration in Groups 2 and 3 and 24 hours prior to GC administration in Group 1 (no trilaciclib). Due to its prolonged half-life, pegfilgrastim may only be used if the patient received Day 8/9 chemotherapy; it should be administered 24 to 48 hours **after the dose of Day 8/9 chemotherapy.**

If in any cycle (including Cycle 1), a patient experiences febrile neutropenia and is at high risk for infection-associated complications OR has prognostic factors that are predictive of poor clinical outcomes (Table 8-2), G-CSF/GM-CSF may be used to treat the febrile neutropenia event per the ASCO guidelines and package insert.

Table 8-2 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

Source: Table recreated from Table 2 of the ASCO guidelines (Smith 2015; Smith 2006)

<u>Erythropoietin stimulating agents (ESAs)</u>

ESAs may not be used in Cycle 1. If a patient experiences a hemoglobin level < 9.0 g/dL or symptomatic anemia in subsequent cycles, ESAs may be used per the current prescribing information (Appendix 4)**.**

8.4.3.4. Dose Modifications for Nonhematologic Toxicity

Section 8.4.3.1 outlines the nonhematologic criteria each patient must meet to receive study drug(s) on Day 1/2 and Day 8/9 of each cycle. All dose reductions will only be made on Day 1/2 of a cycle (Table 8-3). All dose reductions are permanent and no dose increases will occur following a dose reduction. Day 8/9 GC treatment will either be administered at the same dose levels as the Day 1/2 GC doses of that cycle or will be skipped. There will be no Day 8/9 GC dose reductions.

Table 8-3 Dose Modifications for Drug-Related Non-Hematologic Toxicity at Any Point During the Study (All Groups)

		Action Taken			
CTCAE Grade (Gr)	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
AST and/or ALT elevation					
≥ Gr 3	First episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Second episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to 600 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Third episode	Permanently discontinue	Permanently discontinue	Permanently discontinue	

		Action Taken			
CTCAE Grade (Gr)	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
Nausea / vomiting					
Gr 1-2	Any event	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	ALL EVENTS: Manage symptomatically per ASCO Antiemetic Guidelines (2017). Dexamethasone on day of GC dosing permitted but should be limited as much as clinically possible on other days.
≥ Gr 3 despite maximal medical management	First episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Second episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; continue 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to AUC 1.5	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Third episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; Permanently discontinue either gemcitabine or carboplatin and continue the other drug at the reduced dose		Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Fourth episode	Permanently discontinue all study drugs		Permanently discontinue	

		Action Taken			
CTCAE Grade (Gr)	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
Diarrhea					
Gr 1-2	Any event	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	ALL EVENTS: Manage with appropriate antidiarrheal therapy per institutional standards. Patients should be encouraged to take plenty of oral fluids.
≥ Gr 3 despite maximal medical management	First episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Second episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; continue 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to AUC 1.5	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Third episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; permanently discontinue either gemcitabine or carboplatin and continue the other drug at the reduced dose		Permanently discontinue	
	Fourth episode	Permanently discontinue all study drugs		Permanently discontinue	

		Action Taken			
CTCAE Grade (Gr)	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
Other nonhematological toxicity					
Gr 1-2	Any event	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	No change in dose (provided toxicity resolves to ≤ Gr 2 or baseline)	
≥ Gr 3	First episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Second episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; continue 800 mg/m^2	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; reduce to AUC 1.5	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Third episode	Hold drug until toxicity resolves to ≤ Gr 2 or baseline; permanently discontinue either gemcitabine or carboplatin and continue the other drug at the reduced dose		Hold drug until toxicity resolves to ≤ Gr 2 or baseline; no change in dose	
	Fourth episode	Permanently discontinue all study drugs		Permanently discontinue	

		Action Taken			
CTCAE Grade (Gr)	**Toxicity**	**Gemcitabine**	**Carboplatin**	**Trilaciclib**	**Toxicity Management**
Hypersensitivity reaction					
Mild Examples: mild flushing, rash, pruritus Complete infusion as scheduled. Supervise at bedside; no treatment required.	Any event	Manage per institutional guidelines	Manage per institutional guidelines	No change in dose	ALL EVENTS: Careful attention to prophylaxis and bedside monitoring of vital signs is recommended for all subsequent doses (eg rechallenge) following mild/moderate event
Moderate Examples: moderate rash, flushing, mild dyspnea, chest discomfort) Following Gr2 hypersensitivity reaction, patient should **NOT** receive additional trilaciclib, gemcitabine or carboplatin for that cycle. Patient may receive additional doses in subsequent cycles at the discretion of the investigator.	Any event	Manage per institutional guidelines	Manage per institutional guidelines	Stop Infusion. Administer IV antihistamines and IV steroids per institutional standards. Resume infusion at a slower rate (eg, 50% decrease) after recovery of symptoms. If no further symptoms occur after 15 minutes, infusion rate may be increased to the full rate to complete the scheduled full infusion. If symptoms recur, stop infusion.	
Severe Examples: hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)	Any event	Permanently discontinue	Permanently discontinue	Stop infusion immediately. Administer IV antihistamines and IV steroids per institutional standards. Add epinephrine or bronchodilators if indicated. Permanently discontinue	

8.5. Randomization and Blinding

This study is open-label and no blinding will be required.

Patients meeting all inclusion and exclusion criteria will be randomized 1:1:1 to study treatment group by IWRS according to a randomization schedule generated by the statistician. Randomization will be stratified as follows: liver involvement (yes or no) and the number of prior lines of anticancer therapy in the locally recurrent/metastatic setting at the time of randomization (0 or 1-2).

8.6. Prior and Concomitant Medications and Procedures

All concomitant medications including prescription medications, over-the-counter preparations, growth factors, and blood products from informed consent through 30 days after the last dose of study treatment (safety follow-up phone call) will be documented, where possible. Documentation will include information regarding start and stop date(s), dose(s), and reason(s) for the medication use.

Administration of other concomitant nonprotocol anticancer therapies prior to progression is not permitted while on this study. This includes any low-dose systemic chemotherapeutic agent given for a nononcologic purpose (eg, 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 EDC.

Administration of other concomitant investigational agents for any indication is not permitted while on this study.

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.

Trilaciclib is a time-dependent inhibitor of CYP3A4 and is a substrate for CYP3A4. Trilaciclib exposure may be altered by concomitant use of drugs that are strong CYP3A inhibitors or inducers. The exposure of drugs that are CYP3A substrates may be altered by concomitant use of trilaciclib (Section 4.3.2).

- Caution should be exercised with concomitant use of drugs that are strong CYP3A inhibitors (eg, aprepitant, clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, verapamil, and voriconazole).
- Caution should be exercised with concomitant use of drugs that are strong or moderate CYP3A inducers (eg, phenytoin, rifampin, carbamazepine, St John's Wort, bosentan, modafinil, and nafcillin).
- Caution should be exercised with concomitant use of drugs that are extensively metabolized by CYP3A.

Trilaciclib is a potent inhibitor of MATE1, MATE2-K, and OCT2 membrane transporters and therefore caution should be exercised with concomitant use of drugs that are substrates for these transporters (Section 4.3.2).

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.

Necessary supportive care (eg, antiemetics, antidiarrheals) administered per the standard of care at the study center will be permitted. See Section 8.4.3.3 for guidance on the use of growth factors (colony stimulating factors and ESAs) during the trial. 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 GC is allowed per the ASCO guidelines (Hesketh et al. 2017). Use of dexamethasone on Day 2 and 3 should be limited as much as clinically possible.

8.7. Transfusions

Platelets should be transfused at a threshold of ≤ 10,000/μL. Platelets should also be transfused in any patient who is bleeding with a platelet count < 50,000/μL (100,000/μL for central nervous system or ocular bleeding).

Patients with hemoglobin < 8.0 g/dL or with symptomatic anemia can be treated with RBC transfusions at the investigator's discretion.

8.8. Treatment Compliance

The investigator or designee will dispense the study medication, via a pharmacist/designee, only for use by patients enrolled in the study as described in this protocol. The study drug is not to be used for reasons other than those described in this protocol. The investigator or other study staff will supervise each dose of the study drug administered in the clinic. 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, gemcitabine, and carboplatin infusion; and total drug administered in milligrams.

9. STUDY FLOWCHART

The procedures and assessments to be performed during the study are outlined in Table 9-1 (Groups 1 and 2) and Table 9-2 (Group 3).

Table 9-1 Schedule of Assessments for Groups 1 and 2

	Screening	Cycle 1 and Every Odd Cycle[a] (21 days)			Cycle 2 and Every Even Cycle[a] (21 days)			Post-Treatment Visit[b]	Safety Follow-up Phone Call[c]	Survival Follow-up[d]	Post-Treatment Visit + 60 days
Cycle Day	-28	1	8	15 (±1 day)	1	8	15 (±1 day)	22 (last cycle) (+7 days)	(+3 days)	(±7 days)	(±7 days)
Informed Consent	X										
Demographics	X										
Medical History[e]	X										
Eligibility Evaluation	X										
Performance Status	X	X			X			X			
Physical Exam	X	X			X			X			
Vital Signs	X	X[f]	X[f]		X[f]	X[f]		X			
Height/Weight	X[g]	X			X[g1]						
Clinical Chemistry	X	X[h]			X[h]			X			
Hematology[i]	X	X	X	X	X	X	X	X			X
Urinalysis	X										
ECG	X	X[j]									
Pregnancy test[k]	X	X[k]						X			
CCI											
Tumor Assessment	X[m, m1,m2]	CT/MRI of chest/abdomen Q9 weeks through Week 27 and Q12 weeks thereafter. Also include brain MRI if brain metastases present at baseline. Skeletal lesions identified with baseline bone scan to be followed at scheduled visits using localized CT, MRI, or x-ray[m, m1, m2, m3,m4]							Tumor assessment Q12 weeks to continue in Post-Treatment/Follow-up only if patient discontinues study treatment for reason other than PD and has not initiated subsequent anticancer therapy[m,m4]			
Archival Tumor Tissue	X										
PK[n] (optional)		X[n]									
Trilaciclib[o]		X	X		X	X					
GC therapy[p]		X	X		X	X					
CCI											
CCI											
Survival Contact[s]										X	
AEs[t]	X										
Con. Medications	X										

AE = adverse event; ECG = 12-lead electrocardiogram; CCI [redacted] PK = pharmacokinetics, GC therapy= Gemcitabine and Carboplatin therapy; PD = progressive disease

a Study therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator.

b Patients will return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle.

c A safety follow-up contact will be made to each patient at 30 days after the last dose of study treatment to collect AEs and concomitant medications.

d Follow-up should be attempted and documented for each patient that is in the long term Survival Follow-up Phase at least once every 2 months. Patients will be followed for survival until at least 50% of the patients have died. Any anticancer therapies used will be collected.

e Including medical, surgical, radiation history, smoking history, prior systemic anti-cancer therapy, breast cancer history including BRCA classification, screening signs and symptoms within 4 weeks prior to randomization, and medications. Eligibility evaluation and randomization may occur up to 4 days prior to Day 1 Cycle 1 therapy. For all treatment groups, study start is on Cycle 1 Day 1.

f Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be obtained immediately before and after each infusion. Vitals only need to be taken once between each infusion.

g Height will only be measured at the screening visit. Body Surface Area (BSA) will be calculated at Day 1.

g1: BSA (based on actual body weight) will be re-calculated on Day 1 of Cycle 2 and subsequent cycles if weight increases or decreases > 10% from Day 1 of the previous cycle.

h Clinical chemistry (see Section 11.4.2) may be obtained up to 72 hours prior to Day 1 of each cycle.

i Hematology (see Section 11.4.2) may be obtained up to 24 hours prior to dosing on Days 1 and 8 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

j Single 12-lead ECGs will be obtained for all patients at screening. For those patients (Groups 1 and 2) who agree to participate in PK sampling will have ECGs completed in triplicate (at least 1 minute apart) at the following additional time points on Day 1 of Cycle 1: predose (prior to trilaciclib) and at 0.5 hour (end of infusion [EOI] of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

k Female patients of childbearing potential: serum ß-hCG at screening and serum or urine ß-hCG on Day 1 of Cycle 1, Day 1 of every odd cycle, and at the Post-Treatment Visit. A pregnancy test should be obtained within 24 hours of the Cycle 1 Day 1 visit and must be negative to initiate treatment.

CCI [redacted]

m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI with contrast, where clinically possible, of the chest and abdomen at screening (unless obtained within 28 days of dosing), every 9 weeks ± 7 days (Week 9, Week 18 and Week 27) and then every 12 weeks ± 7 days thereafter, until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: Radionuclide bone scans shall be performed at screening. Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Bone scans need not be repeated after baseline unless clinically indicated. Bone scans obtained as standard of care prior to screening will not need to be repeated if performed within 28 days prior to the first dose of study drug(s).

m2. Brain imaging with contrast (by CT or MRI) performed at Screening for all patients. If brain metastases are present at screening, brain imaging shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

m3: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks).

m4: For those patients in the Survival Follow-up Phase who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until the occurrence of progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

n Patients who have agreed to participate in the PK analysis will have blood samples collected on Day 1 of Cycle 1 only at the time points specified in Section 11.2. **The end of infusion (EOI) sample for trilaciclib should be drawn 2 to 5 minutes prior to the trilaciclib EOI.**

o For Group 2: Trilaciclib will be administered as an IV infusion over 30 (±5) minutes prior to GC chemotherapy on Days 1 and 8 of every 21-day cycle (dosing information, see Section 8.1). After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study.

p For Group 1: GC therapy will be administered as an IV infusion on Days 1 and 8 of 21-day cycles (dosing information; see Section 8.1).

For Group 2: GC therapy will be administered as an IV infusion after the trilaciclib infusion (with an interval not greater than 4 hours) on Days 1 and 8 of 21-day cycles (dosing information; see Section 8.1). Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If trilaciclib in any given cycle is not administered for any reason, do not administer the dose of gemcitabine or carboplatin chemotherapy on that day.

CCI

CCI

s Survival follow-up may be a phone contact if subject is not returning to the clinic for tumor assessments.

t AEs will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

Table 9-2 Schedule of Assessments for Group 3

	Screen-ing	Cycle 1 and Every Odd Cycle[a] (21 days)					Cycle 2 and Every Even Cycle[a] (21 days)					Post-Treatment Visit[b]	Safety Follow-up Phone Call[c]	Survival Follow-up[d]	Post-Treatment Visit + 60 days
Cycle Day	-28	1	2	8	9	15 (±1 day)	1	2	8	9	15 (±1 day)	22 (last cycle) (+7 days)	(+3 days)	(±7 days)	(±7 days)
Informed Consent	X														
Demographics	X														
Medical History[e]	X														
Eligibility Evaluation	X														
Performance Status	X	X					X					X			
Physical Exam	X	X					X					X			
Vital Signs	X	X[f]	X[f]	X[f]	X[f]		X[f]	X[f]	X[f]	X[f]		X			
Height/Weight	X[g]	X					X[g1]								
Clinical Chemistry	X	X[h]					X[h]					X			
Hematology[i]	X	X		X		X	X		X		X	X			X
Urinalysis	X														
ECG	X		X[j]												
Pregnancy test[k]	X	X[k]										X			
CCI															
Tumor Assessment	X[m,m1,m2]	CT/MRI of chest/abdomen Q9 weeks through Week 27 and Q12 weeks thereafter. Also include brain MRI if brain metastases present at baseline. Skeletal lesions identified with baseline bone scan to be followed at scheduled visits using localized CT, MRI, or x-ray [m, m1, m2, m3, m4]											Tumor assessment Q12 weeks to continue in Post-Treatment/Follow-up only if patient discontinues study treatment for reason other than PD and has not initiated subsequent anticancer therapy[m,m4]			
Archival Tumor Tissue	X														
PK[n] (optional)			X												
Trilaciclib[o]		X	X	X	X		X	X	X	X					
GC therapy[p]			X		X			X		X					
CCI															
Survival contact[s]														X	
AEs[t]	X														
Con. Medications	X														

AE = adverse event; ECG = 12-lead electrocardiogram; CCI PK = pharmacokinetics, GC therapy= Gemcitabine and Carboplatin therapy; PD = progressive disease

a Study therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator.

b Patients will return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle.

c A safety follow-up contact will be made to each patient at 30 days after the last dose of study treatment to collect AEs and concomitant medications.

d Follow-up should be attempted and documented for each patient that is in the long term Survival Follow-up Phase at least once every 2 months. Patients will be followed for survival until at least 50% of the patients have died. Any anticancer therapies used will be collected.

e Including medical, surgical, radiation history, smoking history, prior systemic anti-cancer therapy, breast cancer history including BRCA classification, documentation of tumor diagnosis, screening signs and symptoms within 4 weeks prior to randomization, and medications. Eligibility evaluation and randomization may occur up to 4 days prior to Day 1 Cycle 1 therapy. For all treatment groups, study start is on Cycle 1 Day 1.

f Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be obtained immediately before and after each infusion. Vitals only need to be taken once between each infusion.

g Height will only be measured at the screening visit. Body Surface Area (BSA) will be calculated at Day 1.

g1: BSA (based on actual body weight) will be re-calculated on Day 1 of Cycle 2 and subsequent cycles if weight increases or decreases >10% from Day 1 of the previous cycle.

h Clinical chemistry (see Section 11.4.2) may be obtained up to 72 hours prior to Day 1 of each cycle.

i Hematology (see Section 11.4.2) may be obtained up to 24 hours prior to GC dosing of on Day 2 or Day 9 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

j Single 12-lead ECGs will be obtained for all patients at screening. Those patients who agree to participate in **PK sampling** will have ECGs completed in triplicate (at least 1 minute apart) at the following additional time points on Day 2 of Cycle 1: predose (prior to trilaciclib) and at 0.5 hour (end of infusion [EOI] of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

k Female patients of childbearing potential: serum ß-hCG at screening and serum or urine ß-hCG on Day 1 of Cycle 1, Day 1 of every odd cycle, and at the Post-Treatment Visit. A pregnancy test should be performed within 24 hours of the Cycle 1 Day 1 visit and must be negative to initiate treatment.

CCI

m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI with contrast, where clinically possible, of the chest and abdomen at screening (unless obtained within 28 days of dosing) every 9 weeks ± 7 days (Week 9, Week 18, and Week 27) and then every 12 weeks ± 7 days thereafter, until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: Radionuclide bone scans shall be performed at screening. Bone scans obtained as standard of care prior to screening will not need to be repeated if performed within 28 days prior to the first dose of study drug(s). Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI, or x-ray. Bone scans need not be repeated after baseline unless clinically indicated.

m2: Brain imaging with contrast (by CT or MRI) performed at Screening for all patients. If brain metastases are present at screening, brain imaging shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

m3: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks).

m4: For those patients in the Survival Follow-up Phase who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality as used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until the occurrence of progressive disease, withdrawal of consent, initiation of anticancer therapy, or study completion.

n Patients who agree to participate in the PK analysis will have blood samples collected on Day 2 of Cycle 1 at the time points specified in Section 11.2. **The end of infusion (EOI) sample for trilaciclib should be drawn 2 to 5 minutes prior to the trilaciclib EOI.**

o For Group 3: trilaciclib will be administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 of every 21-day cycle. Trilaciclib will be administered prior to GC on Days 2 and 9 (dosing information, see Section 8.1). The interval between doses of trilaciclib on successive days should not be greater than 28 hours. After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study.

p For Group 3: GC therapy will be administered as an IV infusion after the trilaciclib infusion (with an interval not greater than 4 hours) on Days 2 and 9 of 21-day cycles (dosing information; see Section 8.1). Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If trilaciclib in any given cycle is not administered for any reason, do not administer the dose of gemcitabine or carboplatin chemotherapy on that day.

CCI [redacted]

CCI [redacted]

s Survival follow-up may be a phone contact if subject is not returning to the clinic for tumor assessments.

t AEs will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

10. SCHEDULE OF STUDY PROCEDURES

Study procedures are summarized across all study visits within the schedule of assessments (Table 9-1 [Groups 1 and 2] and Table 9-2 [Group 3]).

10.1. Screening

Patients should be screened no more than 28 days before the first dose of study treatment is administered. Written informed consent must be obtained from each patient before the initiation of any screening procedures. After a patient has given informed consent, eligibility will be determined by a review of the inclusion/exclusion criteria and completion of all screening procedures outlined in Table 9-1 (Groups 1 and 2) or Table 9-2 (Group 3), and listed below.

- Collection of demographics
- Collection of medical history (including surgical, radiation, smoking, prior systemic anticancer therapies, breast cancer history including BRCA classification)
- ECOG performance status evaluation
- Physical examination
- Height and weight
- Vital signs measurements (blood pressure, heart rate, respiratory rate and body temperature)
- Clinical chemistry, hematology, and urinalysis tests (see Section 11.4.2) (laboratory assessments may be repeated to determine eligibility)
- 12-lead electrocardiogram
- Pregnancy test (serum β-hCG)
- Tumor assessment (chest and abdomen at a minimum by computed tomography [CT] or magnetic resonance imaging [MRI]; see details in Section 11.5.1), including brain and bone scans
- CT, MRI, brain scans, and bone scans obtained prior to informed consent will not need to be repeated if performed within the screening window.
- Available archived tumor samples must be sent to a repository for future assessment of relevant CCI [redacted], such as those involved in the CDK4/6 pathway. For additional guidance regarding the shipment of samples, please refer to the Laboratory Manual.

Adverse events and concomitant medications will be monitored continuously from the time of informed consent through 30 days after the last dose of study treatment (safety follow-up phone call).

Eligibility will be determined prior to randomization. Randomization will be performed within 4 days of the first dose of study treatment. Eligible patients will be instructed on all protocol requirements, including any restrictions on concomitant medication usage.

10.2. Cycle 1 and Subsequent Cycles

Adverse events and concomitant medications will be monitored throughout the study. Safety surveillance reporting of AEs commences at the time informed consent is obtained and continues through 30 days after the last dose of study treatment (safety follow-up phone call).

The timing for critical assessments/procedures is outlined in Table 9-1 (Groups 1 and 2) or Table 9-2 (Group 3). Study treatments will be administered as described in Section 8.1.

Criteria for starting each cycle as well as toxicity management guidelines are outlined in Section 8.4.3.

All Cycles: Days 1 and 8

Predose procedures will be performed and hematology results reviewed (at a minimum) before study drug administration.

Group 1 Assessments:

- ECOG performance status evaluation (predose; **Day 1 only**)
- Physical examination (predose; **Day 1 only**)
- Weight (**Day 1 only**)
- Clinical chemistry (up to 72 hours predose; **Day 1 only**)
- Pregnancy test on Day 1, Cycle 1 and Day 1, Every Odd Cycle. The assessment on Day 1, Cycle 1 must be within 24 hours of the visit and must be negative to initiate treatment.
- Clinical hematology tests (up to 24 hours predose)

CCI [redacted]

- Administer carboplatin and gemcitabine
- Vital signs measurements (immediately before and after each infusion; only needed once between infusions)
- PK Assessments (see Section 11.2) for patients who agree to participate:
  - Blood samples will be collected at predose and 0.5 (carboplatin EOI), 1 (gemcitabine EOI), 2, 3.5, 5, and 24 hours after the start of the carboplatin infusion on **Day 1 of Cycle 1 only** for a minimum of 6 patients

CCI [redacted]

Refer to the laboratory manual for tissue requirements (predose; **Cycle 1 Day 1 only**).

Group 2 Assessments:

- ECOG performance status evaluation (predose; **Day 1 only**)
- Physical examination (predose; **Day 1 only**)
- Weight (**Day 1 only**)
- Clinical chemistry (up to 72 hours predose; **Day 1 only**)
- Pregnancy test on Day 1, Cycle 1 and Day 1, every odd cycle. The assessment on Day 1, Cycle 1 must be within 24 hours of the visit and must be negative to initiate treatment.
- Clinical hematology tests (up to 24 hours predose)

CCI [redacted]

- Administer trilaciclib, carboplatin, and gemcitabine
- Vital signs measurements (immediately before and after each infusion; only needed once between infusions)
- PK Assessments (see Section 11.2 and Section 11.4.5) for patients who agree to participate:
  - Blood samples will be collected at predose and 0.5 (trilaciclib EOI), 1 (carboplatin EOI), 1.5 (gemcitabine EOI), 2.5, 4, 5.5, and 24 hours after the start of the trilaciclib infusion on **Day 1 of Cycle 1 only** for a minimum of 6 patients
  - Electrocardiograms will be performed in triplicate (at least 1 minute apart) at predose, 0.5 hours (EOI of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib only if PK samples are also obtained on **Day 1 of Cycle 1 only**. ECGs should be obtained just prior to PK sampling and after approximately 5 minutes of rest.

CCI [redacted]

Group 3 Assessments:

- ECOG performance status evaluation (predose; **Day 1 only**)

- Physical examination (predose; **Day 1 only**)
- Weight (**Day 1 only**)
- Clinical chemistry (up to 72 hours predose; **Day 1 only**)
- Pregnancy test on Day 1, Cycle 1 and Day 1, every odd cycle. The assessment on Day 1, Cycle 1 must be within 24 hours of the visit and must be negative to initiate treatment.
- Clinical hematology tests (up to 24 hours prior to GC dosing)

CCI

- Administer trilaciclib
- Vital signs measurements (immediately before and after trilaciclib infusion)

CCI

All Cycles: Days 2 and 9

Group 3 Assessments:

- Administer trilaciclib, carboplatin, and gemcitabine
- Vital signs measurements (immediately before and after trilaciclib, carboplatin, and gemcitabine infusions; only needed once between infusions)
- PK Assessments (see Section 11.2 and Section 11.4.5) for patients who agree to participate:
    - Blood samples will be collected at predose and 0.5 (trilaciclib EOI), 1 (carboplatin EOI), 1.5 (gemcitabine EOI), 2.5, 4, 5.5, and 24 hours after the start of the trilaciclib infusion on **Day 2 of Cycle 1 only** for a minimum of 6 patients
    - Electrocardiograms will be performed in triplicate (at least 1 minute apart) at predose, 0.5 hours (EOI of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib only if PK samples are also obtained on **Day 2 of Cycle 1 only.** ECGs should be obtained just prior to PK sampling and after approximately 5 minutes of rest.

All Cycles: Day 15 (± 1 day) (Groups 1, 2 and 3)

- Clinical hematology test

CCI [redacted]

Every 9 Weeks (Groups 1, 2, and 3)

- Tumor assessment (every 9 weeks ± 7 days [Week 9, Week 18, and Week 27]) and then every 12 weeks ± 7 days (beginning Week 39) includes CT or MRI of chest and abdomen (at a minimum) with contrast, if clinically possible; skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan, should be imaged at baseline and followed at scheduled visits using localized CT, MRI, or x-ray. Bone scans need not be repeated after baseline unless clinically indicated. Brain imaging performed only if brain metastases present at baseline or if clinically indicated (eg, patient is symptomatic).

The data monitoring committee (DMC) may recommend decreasing the frequency of hematological evaluations based on accumulating data. The investigators and institutional review boards (IRBs) or independent ethics committees (IECs) will be notified if the frequency is reduced.

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the CCI [redacted]; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study, which is to continue until at least 50% of patients have died.

10.3. Post-Treatment Visit: Day 22 of last cycle

All patients (Groups 1, 2, and 3) may return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle. The following procedures will be performed at this visit:

- ECOG performance status evaluation
- Physical examination
- Vital signs measurements
- Clinical chemistry, hematology, and pregnancy tests
- Tumor assessment (chest and abdomen (at a minimum) CT scan or MRI with contrast (if clinically possible) for patients who have not progressed at the time of study drug discontinuation [may be performed within 4 weeks]); see details in Section 11.5.1) Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Bone scans need not be repeated after baseline unless clinically

indicated. Brain imaging performed only if brain metastases present at baseline or if clinically indicated (eg patient is symptomatic)

CCI [redacted]

10.4. Safety Follow-up Contact: 30 days post last dose

A safety follow-up contact will be made to each patient at 30 days (+3 days) after the last dose of study treatment to collect AEs and concomitant medications. Follow-up can be via telephone, email, clinic visits, or by receiving information from a family member or provider who is administering care.

10.5. Post-Treatment Visit: 60 Days Post Last Dose

All patients (Groups 1, 2, and 3) may return to the study center for a Post-Treatment Visit 60 days (± 7 days) after the last dose of study treatment. The following procedures will be performed at this visit:

- Hematology

CCI [redacted]

After completing the Post-Treatment Visit, patients will enter the long-term Survival Follow-up Phase.

10.6. Survival Follow-up Phase

Follow-up should be attempted and documented for each patient that is in the long-term Survival Follow-up Phase at least once every 2 months (±7 days). Follow-up can be via telephone, email, clinic visits, or by receiving information from a family member or provider who is administering care. Patients will be followed for survival at a minimum until at least 50% of the patients in the study have died.

The following information will be collected for all patients:

- Survival status
- Details of any anticancer treatment

In addition, for patients who have not had disease progression at the time of study drug discontinuation, radiological tumor assessments should be performed utilizing the same modality as used at screening every 12 weeks ± 7 days from the Post-Treatment visit until the occurrence of progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

Patients should not receive other anticancer treatment, or enroll in another therapeutic clinical trial, until after the occurrence of disease progression, and ideally, after the completion of all study visits (including Post-Treatment Visit + 60 days).

10.7. Unscheduled Visits

Additional visits can be performed as appropriate and at the discretion of the investigator. Assessments completed during unscheduled visits will be captured in the eCRF.

11. STUDY ASSESSMENTS

11.1. Efficacy Assessments

Efficacy evaluation will be based on the following: kinetics of changes in CBCs; hematologic toxicities, including febrile neutropenia and infections; RBC and platelet transfusions; hematopoietic growth factor utilization; systemic antibiotic use; chemotherapy dose reductions and dose interruptions; CCI ; CCI ; CCI ; CCI ; and CCI An. All of these variables, except for the CCI , will be assessed as described in the safety assessments (monitoring of AEs, clinical laboratory assessments, study treatment exposure, and concomitant medications) (see Section 11.3, Table 9-1, and Table 9-2). CCI are described in Section 11.6.

The toxicity of trilaciclib administered IV with or without GC therapy will be assessed using the NCI CTCAE, Version 4.03.

11.2. Pharmacokinetic Assessments (Optional)

Serial blood samples will be collected from a minimum of 6 patients enrolled in each group for the measurement of trilaciclib (Groups 2 and 3 only), gemcitabine, and carboplatin concentrations in plasma at the time points outlined below and in Table 9-1 and Table 9-2. Comprehensive information on blood sample acquisition, the specific type of collection tube with anticoagulant, and handling and storage are to be found in the Laboratory Manual. The analytical laboratory will measure plasma concentrations of trilaciclib, gemcitabine, and carboplatin using a validated method. Any remaining sample may be stored long term for the future analysis of trilaciclib drug metabolites.

Cycle 1 Day 1 (Groups 1 and 2)/ Day 2 (Group 3)

Blood samples will be collected for a minimum of 6 patients enrolled in each treatment group on Cycle 1 Day 1 (Groups 1 and 2) or Cycle 1 Day 2 (Group 3) at the time points described in Table 11-1 (for Group 1) and Table 11-2 (for Groups 2 and 3). The actual times in which the samples were drawn will be captured in the eCRF.

Sampling windows per sample number noted in Table 11-1 and Table 11-2:

Group 1:

- Samples 1 – 4: ± 5 minutes
- Samples 5 – 6: ± 10 minutes
- Sample 7: ± 1 hour

Group 2 and Group 3:

- Sample 1: ± 5 minutes
- Sample 2: **2 to 5 minutes prior to the trilaciclib EOI.** Obtaining trilaciclib samples any time after the infusion is complete may result in missing the true C_{max}.
- Samples 3 – 5: ± 5 minutes
- Samples 6 – 7: ± 10 minutes
- Sample 8: ± 1 hour

Table 11-1 Cycle 1 Day 1 (Group 1) Blood Sampling Scheme Based on Predicted Administration Times of Carboplatin and Gemcitabine

Sample Number	1	2	3	4	5	6	7
Sample Time (h)	0 (Predose[a])	0.5 (Carbo EOI)	1.0 (Gem EOI)	2.0	3.5	5.0	24

Carbo = carboplatin; EOI = end of infusion; Gem = gemcitabine; h = hour

Times are approximate; all times are calculated from the start of carboplatin infusion. For simplicity, assumptions were based on 0.5 hour increments. Actual times will be recorded and may vary from those listed here.

a Predose is defined as prior to the first dose of carboplatin in Group 1.

Table 11-2 Cycle 1 Day 1 (Group 2)/ Day 2 (Group 3) Blood Sampling Scheme Based on Predicted Administration Times of Trilaciclib, Carboplatin, and Gemcitabine

Sample Number	1	2	3	4	5	6	7	8
Sample Time (h)	0 (Predose[a])	0.5 (trilaciclib EOI)	1 (Carbo EOI)	1.5 (Gem EOI)	2.5	4.0	5.5	24

Carbo = carboplatin; EOI = end of infusion; Gem = gemcitabine; h = hour

Times are approximate; all times are calculated from the start of trilaciclib infusion. For simplicity, assumptions were based on 0.5 hour increments. Actual times will be recorded and may vary from those listed here.

a Predose is defined as prior to dosing of trilaciclib in Group 2 or Group 3.

Pharmacokinetic Parameters

PK parameters to be derived from trilaciclib, gemcitabine, and/or carboplatin plasma concentration-time data are presented in Table 11-3.

Table 11-3 Pharmacokinetic Parameters

C_{max}	The observed peak plasma concentration determined from the plasma concentration vs. time data
T_{max}	The time to reach the observed peak plasma concentration from the plasma concentration vs. time data
AUC_{0-t}	Area under the plasma concentration-time curve from 0 to t hours after dosing, calculated by linear/log trapezoidal method
λ_z	Terminal phase rate constant, determined by linear regression of at least 3 points on the terminal phase of the log-linear plasma concentration-time curve. The correlation coefficient (r^2) for the goodness of the fit of the regression line through the data points has to be 0.80 or higher, for the value to be considered reliable.
$t_{1/2}$	Terminal half-life, defined as 0.693 divided by λ_z
$AUC_{0-\infty}$	Area under the concentration-time curve from time-zero extrapolated to infinity, calculated as: $AUC\,\text{inf} = AUClast + \frac{Clast}{\lambda z}$ where C_{last} is the last quantifiable concentration in the terminal elimination phase.
CL	Clearance after intravenous administration, calculated as: $CL = \frac{Dose}{AUC_{\text{inf}}}$
Vz	Volume of distribution in the terminal elimination phase, calculated as: $Vz = \frac{CL}{\lambda z}$

11.3. Archival Tumor Tissue

All patients must have tumor tissue available from their TNBC diagnostic sample (archived tissue allowed) to be sent to a central storage facility. Tumor tissue must consist of a minimum of 10 slides or a fixed paraffin block with a depth of at least 40 microns. CCI [redacted] Additional details regarding tumor tissue collection, processing, handling, and shipping may be found in the laboratory manual.

Tumor tissue may be archived for up to 10 years.

11.4. Safety Assessments

Safety evaluations will be conducted as described in Table 9-1 and Table 9-2. Safety evaluations will include monitoring of AEs, vital signs measurements, physical examinations, ECGs, clinical laboratory studies, infusion-related reactions, tumor response and duration of response based on RECIST, Version 1.1 (see Section 11.5), progression-free survival (PFS), and overall survival (OS).

The toxicity of trilaciclib administered IV with or without chemotherapy will be assessed by the investigators using the NCI CTCAE, Version 4.03.

11.4.1. Adverse Events and Serious Adverse Events

11.4.1.1. Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product.

Hematologic toxicity includes neutropenia, lymphopenia, anemia, and thrombocytopenia.

Adverse events include the following:

- All suspected adverse drug reactions (ADRs)
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity
- Apparently unrelated illnesses, including the worsening of a pre-existing illness (see pre-existing conditions below)
- Injury or accidents (Note that if a medical condition is known to have caused the injury or accident [eg, a fall secondary to dizziness], the medical condition [dizziness] and the accident [fall] should be reported as 2 separate AEs). The outcome of the accident (eg, hip fracture secondary to the fall) should be recorded under comments.
- Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test)
- Laboratory abnormalities that are clinically significant and require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (eg, elevated liver enzymes in a patient with jaundice) should be described under comments on the report of the clinical event rather than listed as a separate AE.

An AE does not include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure will be an AE

- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, and/or convenience admission)
- Overdose of either study drug or concomitant medication without any signs or symptoms
- Disease progression

An unexpected AE is any AE that is not identified in nature, severity, or frequency in the current Investigator Brochure or product information.

- An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product). All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. All serious and unexpected ADRs will have expedited reporting to the regulatory agencies following the International Conference on Harmonisation (ICH) requirements

It is the responsibility of the investigator to document all AEs that occur during the study and every effort should be made to remain alert to possible AEs. Patients should be encouraged to report AEs spontaneously or in response to general, nondirected questioning. Adverse events should be reported on the appropriate page of the eCRF.

In the event of an AE, the primary concern is the safety of the patient. If necessary, appropriate medical intervention should be provided, and the investigational drug discontinued.

11.4.1.2. Definition of Serious Adverse Event

The ICH topic E2A on Clinical Safety Data Management, Definitions and Standards for Expedited Reporting defines an SAE as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
  NOTE: 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting (see Section 11.4.1.9) 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 intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such

events are 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.

To ensure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.4.1.3. Assessment of the Severity of Adverse Events

The severity (toxicity grade) of AEs will be graded according to the NCI CTCAE, Version 4.03 (see Appendix 1).

11.4.1.4. Assessment of the Relationship of Adverse Events to Study Drug

The investigator will determine the assessment of the causal relationship of the AE to the study drugs (trilaciclib, carboplatin, and gemcitabine). Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drugs. The following guidance should be taken into consideration when determining causality:

- Temporal relationship of event onset to the initiation of study drugs
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drugs, or reintroduction of study drugs (as applicable)
- Known association of the event with the study drugs or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of nontreatment-related factors that are known to be associated with the occurrence of the event

The following terms for assessment of the causality to study drugs or study procedures are to be used:

- **Unrelated**: There is not a temporal relationship to study drug administration (eg, too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.
- **Unlikely Related**: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE (ie, the AE is doubtfully related to study drug).

- **Possibly Related**: There is a reasonable causal relationship between the study drug and the AE. Information related to withdrawal of study drug is lacking or unclear.
- **Probably Related**: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug. Re-challenge is not required.
- **Definitely Related**: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug, and recurs with re-challenge, when clinically feasible.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

11.4.1.5. Assessment of the Outcome of Adverse Events

The action taken for study drugs (eg, dose not changed, dose reduced, dose interrupted, drug permanently discontinued, dose skipped, dose delayed, not applicable, unknown) will be recorded on the eCRF.

Other actions (eg, none, concomitant medication given, new or prolonged hospitalization, procedural surgery) will also be recorded on the eCRF.

The outcome will be assessed according to the following:

- Fatal
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Recovered/resolved
- Unknown

11.4.1.6. Method, Frequency, and Time Period for Detecting Adverse Events and Serious Adverse Events

Safety surveillance reporting of AEs commences at the time of informed consent and continues through 30 days after the last dose of study treatment (safety follow-up phone call).

For screen failures, only SAEs related to study procedures need be collected and only through the date of screen failure.

11.4.1.7. Documentation of Adverse Events and Serious Adverse Events

All AEs will be documented in the appropriate section of the eCRF. The CTCAE, Version 4.03 grading scale referenced in Appendix 1 is provided to assist in categorizing and grading AEs. All SAEs (see Section 11.4.1.2) will be additionally documented on the SAE report form. For AEs occurring while the patient is in the clinic setting, ie, before, during, or after study drug administration, the start time and stop time of the AE should be recorded in the source document.

The following will be recorded for each AE in the eCRF:

- A description of the AE in medical terms, not as reported by the patient. Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”).
- Date of onset (start date)
- Date of recovery (stop date)
- Grade as assessed by the investigator according to the definitions in the AE Grading Scale. If the AE is not specifically listed in Appendix 1, use the following grades:
  Grade 1 mild
  Grade 2 moderate
  Grade 3 severe
  Grade 4 life-threatening or disabling
  Grade 5 death

11.4.1.8. Adverse Event Coding

Adverse event verbatim terms provided by the investigator will be coded by G1 Therapeutics or its designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) as specified in the statistical analysis plan (SAP).

11.4.1.9. Reporting of Serious Adverse Events

All SAEs must be entered into the SAE form and sent to the medical monitor /drug safety team within 24 hours of first knowledge of the event by the study personnel.

The reporting period for SAEs begins from the time of informed consent through 30 days after the last dose of study treatment (safety follow-up phone call). Any SAE that is thought to be related to the study drug and that occurs after the reporting period must be reported **within 24 hours** of discovery of the SAE.

SAE information will be collected on the eCRFs, therefore it is imperative that any SAE be entered onto the electronic SAE Form within 24 hours of learning of the event. If the EDC system is not operational, the paper SAE Form must be completed within 24 hours and faxed to the number below; if an SAE is faxed, the event must also be entered in EDC once the system is available.

PPD Pharmacovigilance:

US Sites 24 Hour Safety Hotline Fax: PPD

Non-US Sites 24 Hour Safety Hotline Fax: PPD

In the event of fax failure or other reporting questions:

US Sites 24 Hour Safety Hotline: PPD

Non-US Sites 24 Hour Safety Hotline: PPD

In addition, any known untoward event that occurs subsequent to the AE-reporting period that the investigator assesses as related to the investigational medication should also be reported as an AE.

11.4.1.10. Follow-up of Adverse Events

All AEs (both serious and nonserious) will be followed up in accordance with good medical practice until resolution, return to screening, 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 the sponsor.

All unresolved AEs should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained, or further recovery is not deemed to be feasible. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study.

After study conclusion, the investigator should notify G1 Therapeutics of any death or SAE they are aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to the study drug. G1 Therapeutics should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

11.4.1.11. Regulatory Aspects of Adverse Event Reporting

Unexpected serious adverse reactions are subject to expedited reporting to the Food and Drug Administration (FDA) and European National Competent Authorities, the Medicine Evaluation Board, and the Competent Authorities in other Member States, if applicable, in an expedited time frame in compliance with current legislation. The sponsor or its representative will report all unexpected SAEs to the Competent Authority, the Medicine Evaluation Board, and the Competent Authorities in other Member States, as applicable in an expedited time frame.

The investigator is encouraged to discuss with the medical monitor any adverse experiences for which the issue of reportability is unclear or questioned.

It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report. The following information must be reported on the SAE report form:

- Protocol number
- Site and/or investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event has resolved
- Current status, if event has not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of whether the SAE was related to investigative product or not
- Outcome of the event if available

The medical monitor or member of the safety team will contact the site for clarification of data entered in the eCRF and or SAE form, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact the medical monitor or a member of the safety team.

G1 Therapeutics, or their designee, is responsible for submitting reports of AEs associated with the use of the study drug that are both serious and unexpected to the FDA and European National Competent Authorities, the Medicine Evaluation Board, and the Competent Authorities in other Member States, if applicable, in an expedited time frame in compliance with current legislation. Unexpected SAEs that are already reported to the European Medicines Agency Eudravigilance database do not have to be reported again to the relevant authorities. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC.

The expedited reporting will occur no later than 15 calendar days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 days for completion of the final report.

11.4.1.12. Handling of Overdoses and Toxicity

No information on treatment of overdose of trilaciclib is currently available. General supportive measures should be used as appropriate.

11.4.1.13. Reporting of Pregnancies

Pregnancy per se is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication. Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

Each pregnancy in a study patient or partner of a study patient must be reported to the sponsor within 24 hours of learning of its occurrence on the Pregnancy Report Form. If a patient becomes pregnant, study drug administration must be discontinued immediately. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

The avoidance of pregnancy or fathering a child (including sperm donation) is suggested for 6 months following the discontinuation of study drug. No information is currently available regarding the effects of trilaciclib on fertility, gestation, or subsequent child development.

11.4.1.14. Infusion-Related Reactions

An infusion related reaction is defined as “an adverse reaction to the infusion of pharmacological or biological substances” (CTCAE v4.03) and can be divided into two categories: local effects and systemic effects. Those AEs that are infusion related should be recorded in the eCRF as “infusion-related reactions”. Any associated symptoms as outlined in Table 11-4 below should also be recorded as AEs. The associated symptoms and details (ie, local versus systemic) will also be captured in the EDC.

Table 11-4 Symptoms Associated with Infusion-Related Reactions

Redness	Pyrexia	Hoarseness
Edema	Angioedema	Hypoxia
Ulceration	Flushing	Mouth Tingling
Pain	Rigors/Chills	Diaphoresis
Phlebitis	Bronchospasm/Wheezing	Rash (non-specific)
Warmth	Chest Pain	Syncope
Pruritis	Back Pain	Tachycardia
Hypotension	Difficulty Swallowing	Throat Tightness
Shortness of Breath/Dyspnea	Facial Swelling	

11.4.2. Clinical Laboratory Assessments

Blood samples will be collected for clinical laboratory assessments as outlined in Table 9-1 and Table 9-2. The following clinical laboratory tests will be performed:

- Hematology (hemoglobin, white blood cells [WBCs] with differential and platelet counts)
- Chemistry (albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus or phosphate, potassium, total protein, ALT, AST, LDH, sodium, and blood urea nitrogen)
- Urinalysis (semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin; and a microscopic examination, including RBC, WBC, and casts will be performed, if necessary)

Laboratory parameters will be analyzed by a local certified laboratory and laboratory credentials and reference ranges will be sent to the sponsor or designee. The investigator will review all laboratory reports and indicate the clinical significance of all abnormal values, and subsequently sign and file the laboratory report with the patient's source records/charts. Laboratory parameters for which clinically significant values are noted will be re-measured or the appropriate clinical follow-up arranged by the investigator. Values will be documented in the source until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication). Any laboratory value that remains abnormal at the end of the study and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality, or it is deemed that recovery is not feasible.

Laboratory toxicities will be assessed by the investigator using the NCI CTCAE, Version 4.03 (see Appendix 1).

The DMC may recommend decreasing the frequency of hematological evaluations based on accumulating data. The investigators and IRBs or IECs will be notified if the frequency is reduced.

11.4.3. Demographics and Vital Signs

Vital signs should be collected before and after infusion of each study drug; vitals need to be taken only once between infusions. The following will be collected:

- Date of birth
- Age
- Sex
- Ethnicity
- Race
- Height
- Body weight
- Body temperature
- Systolic and diastolic blood pressure, pulse rate, and respiration rate will be measured. Blood pressure should be assessed after 5 minutes of rest, when possible.

11.4.4. Physical Examination

Full physical examination evaluations at screening should include general appearance, skin, breast, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations. Subsequent physical exams should include body systems as appropriate.

Information about the physical examination must be present in the source documentation at the study site. The result of the physical examination prior to the start of study drug must be included in the relevant eCRF. Clinically relevant findings made after the start of study drug, which meet the definition of an AE, must be recorded on the AE eCRF.

11.4.5. Electrocardiogram Assessments

Standard 12-lead ECGs will be performed and assessed locally as outlined in Table 9-1 and Table 9-2. All patients will have single ECGs obtained at Screening.

Additional ECGs will be obtained in triplicate (at least 1 minute apart) for patients in any group who agreed to PK sampling ONLY if PK samples are also obtained. Obtain ECGs on Day 1 (Group 2) and Day 2 (Group 3) for Cycle 1 at the following time points: predose (prior to trilaciclib), 0.5 hour (EOI of trilaciclib), 2 hours (± 10 minutes) after EOI for trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

The investigator or designee should review the ECGs for any abnormalities as compared with predose ECGs.

11.5. Tumor Response

11.5.1. Tumor Assessments

For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening, every 9 weeks ± 7 days (Week 9, Week 18 and Week 27) and then every 12 weeks ± 7 days (beginning Week 39) thereafter, until the occurrence of disease progression, withdrawal of consent, the initiation of subsequent anticancer therapy, or study completion (see Table 9-1 and Table 9-2). Tumor assessments should include CT or MRI with contrast (if clinically possible) of the chest and abdomen.

Radionuclide bone scans shall be performed at screening. Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Bone scans need not be repeated after baseline unless clinically indicated.

Brain scans with contrast (by CT or MRI) shall be performed at screening for all patients. If brain metastases are present at screening, brain scans shall be done with each tumor assessment. If no metastases are present at Screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

Any CT, MRI, bone or brain scans obtained as standard of care prior to screening will not need to be repeated at screening if performed within the screening window.

Assessments should be performed within 7 days of starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. For those patients who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality as used at screening every 12 weeks ± 7 days from the Post-Treatment Visit until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography (PET) is used, it should also be accompanied by spiral CT or MRI.

Investigators should follow the RECIST, Version 1.1 guidelines (Eisenhauer et al. 2009) for tumor assessments.

11.5.2. Tumor Lesions: Identification and Follow-up

11.5.2.1. Measurable Lesions

Measurable tumor lesions are defined as tumor lesions with a longest diameter (measured in at least 1 dimension) with a minimum size as follows (Eisenhauer et al. 2009):

- 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 screening 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 screening, up to 5 measurable tumor lesions/lymph nodes (with a maximum of 2 lesions per organ) should be identified as target lesions that will be followed to quantitate the status of disease during the study. 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. NOTE: malignant lymph node is considered an organ in this study, therefore only 2 malignant lymph nodes may be selected as target lesions and all others should be entered as nontarget lesions.

At screening and each follow-up time point (see Table 9-1 and Table 9-2), each target lesion should be measured and the overall tumor burden will be calculated as the sum of the diameters of the target lesions (longest diameter [LD] for tumor lesions and short axis for lymph nodes) and documented in the eCRF. If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum of the diameters. If multiple lesions coalesce, the LD of the coalesced lesion will be included in the sum of the diameters.

11.5.2.2. Nonmeasurable Lesions

Nonmeasurable lesions include tumor lesions with a longest diameter < 10 mm, lymph nodes with ≥ 10 to < 15 mm short axis, or nonmeasurable 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 (Eisenhauer et al. 2009).

Nontarget lesions: All other lesions (or sites of disease) identified at screening 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.

11.5.2.3. New Lesions

Any new lesions should be identified and recorded at each follow-up assessment, as these are markers of disease progression. As defined in the RECIST, Version 1.1 guidelines (Eisenhauer et al. 2009), new lesions include the following:

- A lesion in an anatomical location that was not scanned at screening
- Equivocal new lesion of small size that with continued therapy and follow-up is found to progress and represent new disease (progression should be considered as of the date of the initial scan)
- Negative positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG-PET) at screening, but has a positive FDG-PET at follow-up
- No FDG-PET at screening and a positive FDG-PET at follow-up that corresponds to a new site of disease as confirmed by CT (date of disease progression should be the date of the initial abnormal FDG-PET scan)

Note: Findings attributable to differences in scanning technique or a change in type of imaging (CT versus MRI) and findings representing something other than tumor (eg, healing or flare of exiting bone lesions, necrosis of a liver lesion) should not be considered new lesions.

11.5.3. Definitions of Tumor Response and Disease Progression

The determination of TNBC tumor response and progression will be based on the RECIST, Version 1.1 criteria (Eisenhauer et al. 2009). The definitions for tumor response per the RECIST, Version 1.1 criteria are as follows:

11.5.3.1. Evaluation of Target Lesion Response

- **Complete response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- **Partial response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the screening sum of diameters.
- **Progressive disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the screening 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. The appearance of 1 or more new lesions is also considered progression.
- **Stable disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

A response category of not evaluable (NE) is to be used when there is inadequate information to otherwise categorize the response status.

11.5.3.2. Evaluation of Nontarget Lesions

- **Complete response (CR)**: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be < 10 mm short axis.
- **Non-CR/Non-PD**: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD)**: Unequivocal progression of existing nontarget lesions or the appearance of at least 1 new lesion.

11.5.3.3. Evaluation of Overall Response

Patients who have at least 1 postdose tumor assessment (CT scan or MRI) will be considered evaluable for tumor response.

Table 11-5 describes the evaluation of overall response at each time point based on target and nontarget lesion responses at each time point, as well as the appearance of new lesions. The best overall response is the best response recorded from the start of the treatment until disease progression. Confirmation of CR and PR is required as described in Sections 11.5.3.1 and 11.5.3.2.

Table 11-5 Evaluation of Overall Response at Each Time Point

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

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable
Source: (Eisenhauer et al. 2009)

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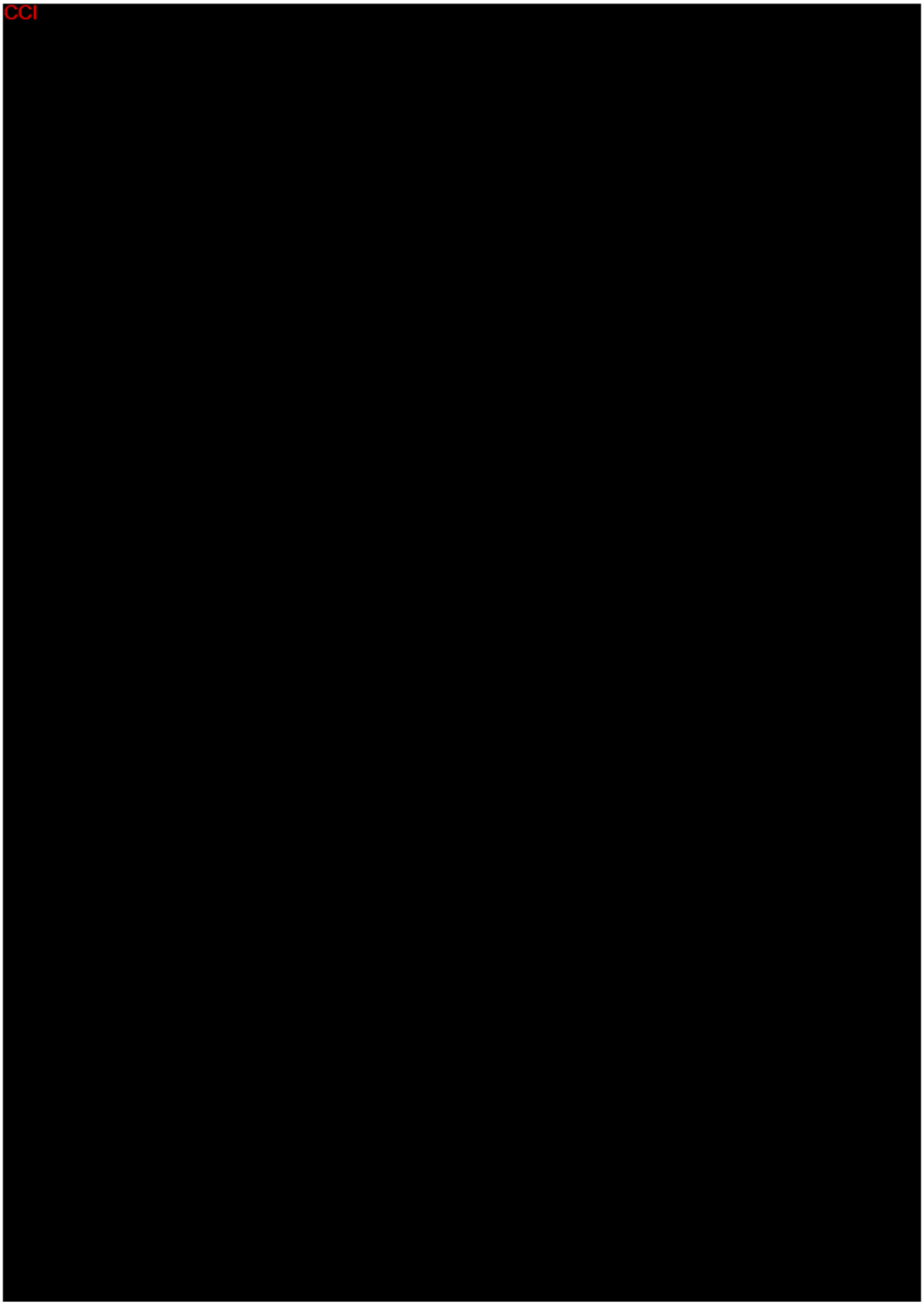

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11.10. Appropriateness of Measurements

The measures of efficacy, PK, and safety evaluated in this study are based on the mechanism and activity of trilaciclib, standard types of assessments typically performed in patients with mTNBC, and prior clinical observations derived from patients receiving GC therapy for mTNBC. The measurement of tumor response based on the RECIST, Version 1.1 (Eisenhauer et al. 2009) is standard. The PK and safety measures included in this study are also standard.

12. STUDY TERMINATION OR STUDY DRUG DISCONTINUATION

12.1. Study Termination

The entire study may be terminated in the event of any of the following:

- Occurrence of AEs unknown to date with respect of their nature, severity, and duration, or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of the drug development program
- Sponsor decision for other reasons

Patients will be followed for survival at a minimum until at least 50% of the patients in the study have died.

12.1.1. Site Termination

A study site will be closed if there is evidence of fraud, other unethical conduct, or significant regulatory noncompliance to the protocol or to Good Clinical Practice (GCP), or if insufficient patients have been enrolled to meet the site objectives.

12.2. Discontinuation of Study Drug

Study drug 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 (eg, a significant intercurrent illness or complication) that, in the judgment of the investigator, are unacceptable for further administration of study drug
- Occurrence of pregnancy
- Significant noncompliance with protocol requirements
- The sponsor or legal representative of the sponsor requests the patient to withdraw
- Patient has radiologically documented disease progression
- If total time between chemotherapy exceeds a total of > 4 weeks, unless agreed to by the treating investigator and medical monitor.
- Where permanent discontinuation of study drug is indicated in the toxicity management recommendations (Table 8-1, Table 8-3).

In the event of study drug discontinuation, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the CCI; the Post-Treatment Visit (Day 22 of last cycle); the safety follow-up contact at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study. A patient who discontinues study treatment for reasons other than PD

will have a CT or MRI scan at the Post-Treatment Visit, if they have not had a scan within the prior 4 weeks.

The investigator will document the reason for study drug discontinuation on the applicable eCRF page.

When discontinuation is due to an AE, the investigator should follow the AE until the events are resolved, the patient is lost to follow-up, the AE is otherwise explained, or further recovery is not deemed to be feasible. Data on these events should be collected on the AE eCRF.

In the event a patient discontinues due to an AE, toxicity, or pregnancy, the investigator should notify the medical monitor by telephone within 48 hours of study drug discontinuation.

A patient can withdraw consent from further treatment/procedures but agree to continue to be followed for survival.

12.3. Withdrawal of Patients from the Study

Patients may withdraw from the study at their own discretion (or at the discretion of the investigator) for any reason at any time. The following list of reasons for withdrawing patients from the study may include but are not limited to:

- Withdrawal of informed consent
- Lost to follow-up (must have at least 2 documented attempts to contact the patient; 1 attempt must be written to the patient and sent via certified letter)

All data and stored laboratory samples collected prior to the date of withdrawal of consent will remain in the clinical database and stored at the laboratory vendor.

13. STATISTICS

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

13.1. Sample Size and Power

The sample size is not determined from a statistical perspective. Approximately 90 patients will be enrolled into the study (30 per treatment group). With 30 patients, the precision for point estimates in each arm is as follows: the 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals are at most the observed proportion +/- 0.167. The 95% CI width for continuous endpoints using the t-distribution are the observed mean +/- 0.373*standard deviation of the endpoint.

13.1.1. Analysis Populations/Sets

The full analysis set (FAS) includes all patients who received at least 1 dose of study drug. Analyses using the FAS will be conducted on the basis of the assigned treatment. All efficacy analyses will be assessed using the FAS and the FAS is the primary population for analysis.

The safety population includes all enrolled patients who received at least 1 dose of study drug. The safety population will be conducted on the basis of the actual treatment received. All safety analyses will be assessed using the safety population.

A per-protocol (PP) subset may also be used to analyze select endpoints and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations.

The PK set will include all dosed patients with evaluable PK data.

13.1.2. Timing of Analyses

13.1.2.1. Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DMC) will monitor accumulating safety data according to a charter that defines its roles and responsibilities. The first DMC meeting will occur after approximately the first 20 patients have been enrolled and completed at least 1 cycle. The DMC will perform interim reviews approximately every 4 months during the Treatment Phase, depending upon the enrollment rate. Additional reviews may occur based on DMC requests. The committee will consist of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, TNBC) and biostatistics. These individuals will be entirely independent of the conduct of the study.

Additional details regarding the committee procedures and policies, including table displays and strategy for maintaining study blind, are described in the DMC charter.

No interim analyses of efficacy are planned.

13.1.2.2. Final Analysis

The final analysis will occur when the last patient completes the Post-Treatment Visit. All study data collected up through the time of the final analysis data cut, including the Survival Follow-up Phase results, will be included in the final analysis.

13.1.2.3. End of Study Analysis

If the Survival Follow-up Phase of the study continues after the final analysis, a supplementary analysis will be done at the time of study completion. Reported results will be cumulative in nature, including all data collected during the entire study.

13.1.3. General Considerations for Data Analysis

All statistical analyses will be performed using SAS® version 9 or higher.

Data will be summarized descriptively by treatment group and for combined treatment Groups 2 and 3. Treatment differences between the GC therapy (Group 1) and each of the other treatment groups (Groups 2 and 3) will be estimated. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, and minimum and maximum values. The descriptive summaries of time-to-event data will include median, twenty-fifth and seventy-fifth percentiles, and standard error. All data will be listed for all patients. Unless specified otherwise, safety summaries will include all collected data, and summaries of efficacy will include data collected through the Treatment Phase.

This study is descriptive in nature, and no formal hypothesis testing will be performed across treatment groups. All CIs will be 95%, unless stated otherwise.

The effects of covariates and withdrawal from study treatment due to reasons other than death, disease progression, and toxicity will be assessed to determine the impact on the general applicability of results from this study. Further details of the analysis, including the handling of missing data, impact of variable chemotherapy dose exposure including dose reductions, transformations and other data handling procedures will be provided in the SAP.
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13.2. Baseline and Demographic Characteristics

Demographics and baseline (screening) characteristics will be summarized descriptively.

13.3. Efficacy Analysis

13.3.1. Efficacy Endpoints

Unless otherwise stated, the terminology 'hematologic parameters' refers to ANC, lymphocyte, hemoglobin, and platelet counts; the terminology 'hematologic toxicities' refers to neutropenia, lymphopenia, anemia, and thrombocytopenia. Each parameter and toxicity

will be evaluated individually, but are described as such to avoid repetition. Hematologic toxicities are assigned based on CTCAE, Version 4.03.

- Hematologic kinetic endpoints:

  - Change and percent change in hematologic parameter values from screening to the Post-Treatment Visit
  - Change and percent change in hematologic parameter values from predose for a particular cycle to the end of that cycle
  - Change and percent change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
  - Rate of change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
  - Change and percent change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
  - Rate of change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
  - Area under the curve in hematologic parameter values from predose for a particular cycle to the end of that cycle
  - Area under the curve in hematologic parameters from predose for a particular cycle to nadir for that cycle
  - Area under the curve in hematologic parameter values from nadir for a particular cycle to the end of that cycle
  - By cycle and overall study hematologic parameter nadir values
  - Time to hematologic parameter value nadir by cycle
  - Time to return to predose hematologic parameter values by cycle
  - Proportion of patients with a return to predose hematologic parameter values by cycle

- Hematologic toxicity endpoints:

  - Incidence of Grade 3 and 4 hematologic toxicities
  - Total number of Grade 3 and 4 hematologic toxicities
  - Proportion of patients with a hematologic toxicity recovery by cycle
  - Time to hematologic toxicity recovery by cycle

- Chemotherapy exposure and compliance endpoints:

  - Duration on treatment
  - Number of cycles received
  - Dose intensity and cumulative dose
  - Incidence of dose interruptions, delays, and reductions
  - Incidence of dose delays due to hematologic toxicity
  - Incidence of study treatment termination due to hematologic toxicity

- Other efficacy endpoints:

- Incidence of infections overall and by severity
- Incidence of RBC and platelet transfusions
- Incidence of hematopoietic growth factors use
- Incidence and duration of systemic antibiotic use

13.3.2. Methods of Analysis for Efficacy Endpoints

Summaries of efficacy will be performed using the FAS. Select summaries will also be repeated in the PP analysis set. Stratification factors will be included as covariates, unless otherwise specified, in the applicable statistical modeling analyses. Unless noted otherwise, hematologic endpoints will be summarized separately by each parameter type (ie, ANC, lymphocytes, etc.). The SAP will describe in detail the minimum sampling and dosing requirements for inclusion in the analysis of each endpoint for a given cycle or overall, particularly for those that involve AUC, nadir, and end of cycle results. Sensitivity analyses may be performed to assess the impact of incomplete dosing within a cycle or missing sampling times.

13.3.2.1. Analysis of Hematologic Parameter Kinetic Endpoints

Hematologic parameter values will be tabulated with descriptive statistics using absolute counts, change, and percent change values. By-visit tabulations will include values at study screening (ie, prior to first dose of study treatment) and each postscreening visit through all cycles and 22 (+ 7 days) days after the last dose of study treatment. Changes and percent changes will be calculated at each postscreening value. Additional tabulations for each cycle of treatment will include predose, nadir, maximum postnadir, and end of cycle values. The change and percent changes from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle values will also be tabulated for each cycle of treatment. Analysis of covariance (ANCOVA) models will be performed separately at each visit and for each of the following parameters as dependent variables: change from screening

and percent change from screening. Analysis of covariance models will be performed separately at each cycle and for each of the following parameters as dependent variables: predose (for cycles 2 and onward), nadir, the Post-Treatment Visit counts, change from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle; and percent change from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle. The models will include terms for treatment, the stratification factors, and screening hematologic parameter value. The least square (LS) mean for each treatment group and LS mean difference between treatment groups will be reported. Two-sided 95% CIs will be constructed around the LS mean differences in treatment groups.

The most extreme Treatment Phase nadir value and the cycle at which the most extreme nadir occurred will be summarized descriptively. Time to nadir will be summarized descriptively for each cycle and is calculated for each cycle and defined as date of nadir minus predose date + 1.

The AUC in hematologic parameters will be tabulated for each cycle, separately for the following windows within a cycle: predose to end of cycle (AUC_{EOC}), predose to nadir (AUC_{Nadir}), and nadir to end of cycle (AUC_{NEOC}). Analysis of covariance models similar to those described above will be performed separately at each cycle using each of the AUC parameters as dependent variables. Additionally, a repeated-measures model of AUC parameters over all cycles will be performed for each AUC measure separately, with fixed effects for treatment, treatment cycle, treatment by cycle interaction, screening hematologic value, and the stratification factors. The unstructured covariance model will be used to tabulate the LS means for each treatment group and the LS mean difference between treatment groups at each cycle. Two-sided 95% CIs will be constructed around the LS mean differences in AUC between treatment groups. An analysis accounting for cumulative dose exposure at each cycle will be performed to support the evaluation of AUC over cycles.

The proportion of patients that return to predose values will be summarized by cycle for each hematologic parameter. Percentages for by-cycle summaries will be based on the number of patients treated in the cycle. For tabulations performed based on data collected, the difference in rates between treatment groups will be calculated. Two-sided 95% CIs will be constructed around the difference in treatment groups. If there are substantial dose reductions, an incidence rate, adjusting for cumulative exposure, may be reported to account for differing amount of exposure by cycle.

Time to return to predose levels will be estimated for each cycle using the Kaplan-Meier method. Time to return to predose levels is defined for all patients as the number of days from nadir to the first postnadir date of levels greater or equal to predose levels prior to end of cycle. A clinically meaningful +/- predose level window will be defined for each hematologic parameter and specified in the SAP. Time to return to postnadir predose levels is also calculated from the start of the cycle (first dose in the cycle). Patients who do not return to predose levels within the window will be censored at the last date with nonmissing results. The same analysis will be repeated on the subset of patients that had a Grade 3 or higher toxicity.

13.3.2.2. Analysis of Hematologic Toxicity Endpoints

The number and percentage of patients with Grade 3 and 4 hematologic toxicities at each cycle and overall during the Treatment Phase will be tabulated for each type of hematologic toxicity and across all type of hematologic toxicities. Percentages for by-cycle summaries will be based on the number of patients treated in the cycle. For tabulations performed based on data collected, the difference in rates between treatment groups will be calculated. Two-sided 95% CIs will be constructed around the difference in treatment groups. If there are substantial dose reductions, an incidence rate, adjusting for cumulative exposure, may be reported to account for differing amount of exposure by cycle.

The total number of Grade 3 and 4 hematologic toxicities will be summed over the entire Treatment Phase per patient, separately for each type of hematologic toxicity and across all types of hematologic toxicities. To account for differing amount of exposure, a toxicity rate will be calculated for each patient, and defined relative to cumulative exposure (total number of toxicities divided by cumulative exposure). A recurrent events model may be performed to estimate the incidence of Grade 3 or higher hematologic toxicities and test for the difference between treatment groups.

For each hematologic parameter and cycle, the following shift summaries will be performed: from predose toxicity to maximum on treatment toxicity; from predose toxicity to end of cycle toxicity; from maximum postdose toxicity to end of cycle toxicity.

Hematologic recovery will be defined in the SAP. The number and percentage of patients with hematologic recovery will be calculated at each cycle. Time to postdose recovery within a cycle will be estimated using the Kaplan-Meier method. A Cox proportional hazard model adjusted for screening hematologic toxicity and the stratification factors will also be performed.

13.3.2.3. Analysis of Chemotherapy Exposure and Compliance

The following parameters will be summarized by treatment group and overall: total duration of treatment, total number of cycles received, cumulative dose of GC therapy received, and number and percentage patients experiencing one or more doses delayed, skipped, interrupted, and reduced. Additionally, the number and percentage of doses delayed, skipped, interrupted and reduced will be summarized. The following parameters will be summarized for each cycle by treatment group and overall: number and percentage of patients receiving dose at the cycle, experiencing one or more dose delay, interruption, and reduction, and cumulative dose of GC therapy received. The number and percentage of patients experiencing a treatment cycle delay due to a hematologic toxicity will be summarized by cycle and overall. The number and percentage of patients discontinuing study treatment due to a hematologic toxicity and cycle of discontinuation will also be summarized.

13.3.2.4. Other Efficacy Endpoints

Infections, RBC and platelet transfusions, systemic antibiotic use, and hematopoietic growth factor use will be summarized with the number and percentage of patients experiencing the event any time during the Treatment Phase of the study. For tabulations performed based on

data collected, the difference between treatment groups will be calculated and reported as described for the incidence of hematologic endpoints.

The number and percent of infections will also be summarized by maximum severity. The infection rate will be calculated as the number of infections occurring during the Treatment Phase divided by cumulative exposure.

13.4. Safety Analysis

13.4.1. Safety Endpoints

- Incidence of treatment-emergent AEs, SAEs, related AEs, related SAEs, and AEs leading to study drug discontinuation
- Infusion-related reactions
- Vital signs
- Physical examination
- ECG readings
- Clinical hematology, chemistry, and urinalysis results
- Concomitant medications
- Tumor response, duration of response, and best overall response based on RECIST, Version 1.1
- Progression-free survival

- Overall survival

13.4.2. Methods of Analysis for Safety Endpoints

The safety analysis will be performed in all patients who have received at least 1 dose of study drug. Adverse event data will be coded to system organ class and preferred term using MedDRA (Version 17.1, or later). Treatment emergence is defined as any AE occurring on or after the day of first dose through 30 days after the last dose of study treatment. The number and percentage of patients experiencing any treatment-emergent AE overall and by system organ class and preferred term will be tabulated. The incidence rates by cycle and adjusted by exposure time will also be presented. Each AE will be counted only once for a given patient at each level of summarization. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. Infusion-related reactions will be tabulated separately from the AEs.

Absolute values and changes from screening in vital signs, ECG readings, and hematology and clinical chemistry parameters will be tabulated at each visit during the Treatment Phase. Toxicities for clinical labs will be characterized according to the CTCAE, Version 4.03. Shifts in toxicity grades from screening to each visit will be summarized.

Overall disease responses as determined by RECIST, Version 1.1 will be summarized by response level at each visit and best overall response. The number of patients with a confirmed objective disease response, defined as patients with a best overall response of confirmed CR or PR obtained during the Treatment Phase, will be summarized.

Progression-free survival is measured from date of first dose date until date of documented disease progression or death and will be estimated using the Kaplan-Meier method. Patients who have not died or had documented disease progression at the time of analysis will be censored on the last on-study date with nonmissing tumor response data.

Overall survival is measured from first dose of trilaciclib until death and will be estimated using the Kaplan-Meier method. Patients alive at the time of analysis will be censored on the last date the patient was known to be alive.

Censoring techniques that account for missing tumor assessments and potential differences in the duration of time patient has on study tumor assessments may be applied for PFS data. The methods will be described in the SAP.

CCI

CCI [redacted]

13.6. Pharmacokinetic Analysis

PK analyses will be based on the PK set, and all analysis and reporting of plasma concentration and PK parameter data will be performed separately for each analyte.

Serial blood samples will be collected from a minimum of 18 patients total, 6 from each treatment group, on Day 1 (Groups 1 and 2) or Day 2 (Group 3) of Cycle 1 to determine trilaciclib, gemcitabine, and carboplatin plasma concentrations. Plasma concentration data will be tabulated descriptively and graphed at each visit and time point. PK parameters will be calculated with noncompartmental methods (WinNonlin Version 6.3 or higher) based on the plasma concentration-time data. The following PK parameters will be calculated (when data permit their calculation): C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, clearance (CL), and V_z. PK parameters will be summarized descriptively by visit and analyte.

CCI [redacted]

CCI [redacted]

14. QUALITY CONTROL AND QUALITY ASSURANCE

An eCRF must be completed for each patient enrolled. Each completed eCRF, as well as records for those patients who discontinue the study, will require a signature by the principal investigator at the study site. If a patient withdraws from the study, the reason must be noted on the eCRF, and if a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug-dispensing log by the investigator.

A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator. As patients complete the study (or withdraw) and their signed eCRFs become available for review, a comparison check will be run to identify and resolve any discrepancies in the data base.

15. ETHICS AND PROTECTION OF HUMAN PATIENTS

15.1. Ethical Conduct Statement

The investigator will ensure that this study is conducted in full conformance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The investigator will ensure adherence to the basic principles of GCP as outlined in the current version of 21 CFR, subchapter D, Part 312, Responsibilities of Sponsors and Investigators, part 50, Protection of Human Subjects, and Part 56, Institutional Review Boards, and ICH E6 GCP. The investigator will follow all national, state, and local laws of the pertinent regulatory authorities.

15.2. Institutional Review Board/Independent Ethics Committee

The protocol and all associated amendments and consent/assent materials will be reviewed and approved by the investigative site's local or a central IRB or IEC. It is the investigator's responsibility to obtain approval of the study protocol and informed consent, and any other study related materials such as advertising or information leaflets, from their IRB/IEC prior to initiating the study. Approval must be obtained in writing via a letter identifying the protocol, the date of the IRB/IEC meeting, and the date of approval. Any modifications made to the protocol after receipt of the IRB/IEC approval must also be submitted by the investigator to the IRB/IEC in accordance with local procedures and regulatory requirements. Any updates to the protocol should receive IRB/IEC approval or favorable opinion, which should be documented in a letter to the investigator, prior to implementation.

15.3. Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of the goals, methods, potential benefits, and hazards of the study. The investigator or designee must also explain that the patients are allowed to withdraw from the study at any time and for any reason. All patients should be given a copy of the informed consent and any updates. Original signed consent forms will be maintained at the site and be made available for inspection, as appropriate.

15.4. Patient Confidentiality

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. Patient names will not be supplied to the sponsor and only the patient number will be recorded in the eCRF and study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

15.5. Adherence to the Protocol

The study shall be conducted as described in this protocol, except for an emergency situation in which proper care of the patient requires immediate alternative intervention. The sponsor will provide this protocol to the IRB/IEC and appropriate local regulatory authorities for approval. Any protocol amendments will be done in accordance with the provisions agreed upon in Section 15.6. Any deviation from the design of the study as set forth in this document will be recorded as a protocol deviation and will be explained in detail as it occurs and/or is detected.

15.6. Protocol Amendments

Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the sponsor.

All protocol modifications (both nonsubstantial and substantial amendments) must be submitted to the appropriate IRB/IEC for information in accordance with local requirements. Approval must be received before changes can be implemented (ie, if the risk benefit ratio is affected and/or the modification represents a change in basic trial definitions such as objectives, design, sample size, and outcome measures, etc.), except for those changes which would decrease risk to the patient. All substantial protocol amendments must have approval from the relevant competent regulatory authority before changes can be implemented.

15.7. Patient Compliance

Patients must be available for all scheduled study visits. Any reason for patient noncompliance will be documented.

15.8. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time, according to the terms specified in the study contract. The investigator should notify the IRB/IEC in writing of the study's completion or early termination. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

16. DATA HANDLING AND RECORD KEEPING

16.1. Data Collection and Retrieval

This study will use a 21 CFR Part 11 compliant electronic data capture system. An eCRF will be used for data recording. All data requested on the eCRF must be entered and all missing data must be accounted for.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against the investigator's records by the study monitor (source document verification), and the maintenance of a study drug-dispensing log by the investigator.

Before study initiation, at a site initiation visit or at an investigator's meeting, a sponsor representative will review the protocol and eCRFs with the investigators and their staff. During the study, a monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, and the progress of screening and randomization. The monitor will ensure during on-site visits that study medication is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitors during these visits.

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are to be performed according to the study-specific monitoring plan.

16.2. Data Monitoring Committee

An external DMC will be used to evaluate safety of the study in an ongoing manner (see Section 13.1.2.1 for further details).

16.3. Investigator Reporting Requirements

Local regulations may require the investigator to provide periodic safety updates on the conduct of the study and to notify the IRB/IEC of study closure. Such updates and notifications are the responsibility of the investigator.

16.4. Records Retention

After closure of the study, the investigator will maintain copies of all study records (ie, investigator files and patient files) in a secure location. The investigator's study file will contain the protocol, protocol amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff

curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents may include (but not limited to) patient hospital records, physician's and nurse's notes, original laboratory reports, ECG, X-ray, signed informed consent forms, consultant letters, and patient screening and randomization logs.

These documents must be kept on file by the investigator for a period of 2 years following the date the marketing application is approved for the drug indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, all records pertaining to the conduct of the clinical study must be adequately maintained until 2 years after the investigation is discontinued and the regulatory authorities are notified. After that period of time, the documents may be destroyed, subject to local regulations.

The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss or destruction of any study records and should notify the sponsor of any reassignment of study records to another party or move to another location.

16.5. Study Monitoring

Qualified representatives of the sponsor or sponsor designees (study monitors) will monitor the study according to a predetermined monitoring plan. The investigator must permit the study monitors to periodically review all eCRFs and source documents supporting the participation of each patient in the study. The eCRFs and other documentation supporting the study must be kept up to date by the investigator and the staff at the study site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor, at each monitoring visit and must be provided in a way such that the patient’s confidentiality is maintained in accordance with local institution, state, country, and federal requirements.

16.6. Audits and Inspections

At some point during the study or after the study, appropriately qualified personnel from the sponsor’s Quality Assurance group, or their authorized representative, or a representative from a regulatory authority may visit the investigator to conduct an inspection of the study and the site. During this audit, the investigator agrees to give the auditor direct access to all relevant documents supporting the eCRFs and other study-related documents and to discuss any findings with the auditor. In the event of an inspection by a regulatory agency, the investigator agrees to give the inspector direct access to all relevant documents and to discuss any findings with the inspector.

17. 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 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.

At least 60 days prior to expected submission to the intended publisher or meeting committee, the investigator will submit a copy of the desired presentation (oral or written) or publication manuscript to the sponsor. This review period may be shortened upon mutual consent where circumstances require expeditious review. The sponsor 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. The sponsor shall determine order of authorship of any publication combining all clinical results of this trial.

18. REFERENCES

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19. APPENDICES

APPENDIX 1: Common Terminology Criteria for Adverse Events (CTCAE) –Version 4.03

The NCI CTCAE Version 4.03 (CTCAE 4.03 14 June 2010) can be accessed from the following National Cancer Institute (NCI) website:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX 2: Package Inserts for Chemotherapy Agents

Gemzar® (gemcitabine) package insert link:
https://pi.lilly.com/us/gemzar.pdf

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. August 2012. Accessed at:
https://www.medicines.org.uk/emc/medicine/27136

Paraplatin® (carboplatin) package insert link:
http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_03_05_Carboplatin%20label%201-9-04%20FDA.pdf

Carboplatin 10 mg/mL concentrate for infusion. Summary of Product Characteristics. April 2016. Accessed at: http://www.medicines.org.uk/emcmobile/medicine/25716

APPENDIX 3: Package Inserts for Colony Stimulating Factors

Neupogen® (filgrastim) package insert link:
http://pi.amgen.com/united_states/neupogen/neupogen_pi_hcp_english.pdf

Neulasta® (pegfilgrastim) package insert link:

http://pi.amgen.com/united_states/neulasta/neulasta_pi_hcp_english.pdf

APPENDIX 4: Package Inserts for Erythropoiesis Stimulating Agents

Aranesp® (darbepoetin alfa) package insert link:
http://pi.amgen.com/united_states/aranesp/ckd/aranesp_pi_hcp_english.pdf

Epogen® (epoetin alfa) package insert link:

http://pi.amgen.com/united_states/epogen/epogen_pi_hcp_english.pdf