Protocol Title: A Phase 2, Single-Arm, Open-Label Study of Trilaciclib Administered Prior to Sacituzumab Govitecan-hziy in Patients with Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments, at Least One in the Metastatic Setting

Protocol Number: G1T28-213

Compound: Trilaciclib

Study Phase: 2

Sponsor Name: G1 Therapeutics, Inc.

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Regulatory Agency Identifier Numbers: IND: 145091

Approval Date: 15 Nov 2021 (Version 2.0)

Previous Version: 29 Jun 2021 (Version 1.0)

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

I have read and understand the contents of this clinical protocol, Version 2.0 for Study G1T28-213 dated 15 Nov 2021 and I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of the study.

PPD

11/15/2021

PPD PPD

Date

PPD PPD

G1 Therapeutics, Inc.

INVESTIGATOR'S AGREEMENT

Clinical Study Protocol G1T28-213: A Phase 2, Single-Arm, Open-Label Study of Trilaciclib Administered Prior to Sacituzumab Govitecan-hziy in Patients with Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments, at Least One in the Metastatic Setting

Version 2.0 Issue Date: 15 Nov 2021

I have read the G1T28-213 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Principal Investigator Signature	Date
Principal Investigator Name	Institution

1. SYNOPSIS

Name of Sponsor/Company: G1 Therapeutics, Inc.		
Name of Investigational Product: Trilaciclib for Injection, 300 mg/vial		
Name of Active Ingredient: trilaciclib (G1T28)		
Protocol Number: G1T28-213	**Phase:** 2	**Region:** United States
Title of Study: A Phase 2, Single-Arm, Open-Label Study of Trilaciclib Administered Prior to Sacituzumab Govitecan-hziy in Patients with Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments, at Least One in the Metastatic Setting		
Study centers: Approximately 20 centers		
Study period (months): Approximately 30 months Estimated date first patient enrolled: Q4 2021 Estimated date last patient completed: Q2 2024		
Objectives: **Primary:** To evaluate the anti-tumor efficacy of trilaciclib when administered prior to sacituzumab govitecan-hziy as measured by progression-free survival (PFS). **Secondary:** To evaluate the anti-tumor efficacy of trilaciclib administered prior to sacituzumab govitecan-hziy as measured by the objective response rate (ORR), duration of objective response (DOR), clinical benefit rate (CBR), and overall survival (OS); evaluate the myeloprotective effects of trilaciclib; and assess the safety and tolerability of trilaciclib administered prior to sacituzumab govitecan-hziy		
Study Design: This is a Phase 2, multicenter, open-label, single arm study evaluating the safety and efficacy of trilaciclib administered prior to sacituzumab govitecan-hziy in patients with unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC) who received at least 2 prior treatments, at least 1 in the metastatic setting. Approximately 45 patients will be enrolled. Trilaciclib and sacituzumab govitecan-hziy will be administered intravenously (IV) in 21-day cycles as indicated in the respective dosage and administration sections of the synopsis. A Safety Monitoring Committee (SMC) will monitor accumulating safety and disposition data with the first meeting planned when approximately 10 patients have completed at least 2 cycles of study treatment. The meetings will continue when approximately 25 enrolled patients have completed at least 2 cycles of study treatment and again when all enrolled patients have completed at least 2 cycles of study treatment or as defined in the SMC charter. Additional reviews may occur. The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of the first dose of study treatment and completes at the Safety Follow-up Visit. The first Survival Follow-up assessment should occur approximately 3 months after the Safety Follow-Up Visit. Study drug administration will continue until progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or clinical progression as determined by the Investigator, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the study, whichever occurs first. Treatment cycles will occur consecutively without interruption, except		

when necessary, to manage toxicities or for administrative reasons. A 3-week delay from the scheduled dose of sacituzumab govitecan-hziy is permitted. As examples, if at the scheduled Cycle X Day 1 visit (e.g., Cycle 2 Day 1) a dose delay is needed for toxicity reasons, a delay up to 3 weeks from Cycle X Day 1 for sacituzumab govitecan-hziy is permitted; if at the scheduled Cycle X Day 8 visit (e.g., Cycle 1 Day 8) a dose delay is needed for toxicity reasons, a delay up to 3 weeks from Cycle X Day 1 for sacituzumab govitecan-hziy is permitted. A dosing delay >3 weeks from the scheduled dose of sacituzumab govitecan-hziy may be permitted on a case-by-case basis with the approval of the Investigator and Medical Monitor. Criteria that patients must meet in order to receive study treatment are provided in the full protocol.

An End of Treatment Visit will occur approximately 14 days following a patient's last dose of study treatment. A Safety Follow-up visit (which may be a phone call) will occur 30 days after the last dose of study drug. Following the Safety Follow-up Visit, patients will be followed for survival approximately every 3 months. These survival follow-ups may be done via telephone, email, or clinic visit. Unless otherwise decided by the Sponsor, the study will continue until at least approximately 70% of patients enrolled in the study have died.

Methodology:

Sample Size Justification:

The sample size is calculated to support the primary objective of the study, that is, to evaluate trilaciclib's effect on PFS when administered prior to sacituzumab govitecan-hziy in patients with unresectable locally advanced or metastatic TNBC who received at least 2 prior treatments with at least 1 in the metastatic setting.

This single-arm study plans to enroll 45 patients during a 10-month accrual period with an approximate 30-month total study duration. With 45 patients and 14 months of follow-up after the last patient is dosed, the following table presents the required number of PFS events and statistical power to detect hazard ratios of 0.7 and 0.8 at a 2-sided significance of 0.2 for a median PFS of the historical control group of 5.6 months, which was observed in patients without brain metastases treated with sacituzumab govitecan-hziy in the Phase 3 ASCENT trial (Bardia, 2021). The calculation is based on a one-sample log-rank test (Wu, 2015) with the assumption that the survival time distributions for both study treatment and historical control group follow the Weibull distribution with a shape parameter of 1.00 (i.e., exponential distribution).

Hazard Ratio	Median PFS for trilaciclib + sacituzumab govitecan-hziy (Months)	Expected number of events in the study	Statistical Power
0.70	8.0	36	80%
0.80	7.0	38	54%

Number of patients (planned):

Approximately 45 patients are planned in this study.

Diagnosis and main criteria for inclusion:

Patients ≥18 years of age at the time of signing the informed consent with measurable locally advanced, unresectable, or metastatic TNBC (defined as <1% estrogen receptor and progesterone receptor by immunohistochemistry [IHC], human epidermal growth factor receptor 2-negative by IHC or in situ hybridization) and with an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients must have measurable disease as defined by RECIST v1.1 and considered eligible to receive sacituzumab govitecan-hziy treatment. Patients with known brain metastasis at the time of enrollment are not eligible. Patients must have received 2 or more prior lines of systemic therapy, at least one of them in the metastatic setting. Prior radiation therapy is permitted

for recurrent disease as long as the patient has at least 1 measurable lesion that has not been irradiated. Patients must also have adequate organ function as demonstrated by laboratory values.

Investigational product, dosage, and mode of administration:

Trilaciclib

In each 21-day cycle at Day 1 and Day 8, a dose of trilaciclib 240 mg/m^2 reconstituted and diluted in 250 mL of sodium chloride solution 0.9% (normal saline) or dextrose 5% in water (D5W) will be administered as a 30-minute IV infusion completed within 4 hours prior to start of sacituzumab govitecan-hziy each day sacituzumab govitecan-hziy is administered. If administration of sacituzumab govitecan-hziy is skipped or discontinued, trilaciclib will also be skipped or discontinued.

Duration of treatment:

Study treatment administration will continue for each patient until progressive disease per RECIST v1.1 or clinical progression as determined by the Investigator, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever occurs first.

Reference therapy, dosage, and mode of administration:

In each 21-day cycle at Day 1 and Day 8, a dose of sacituzumab govitecan-hziy 10 mg/kg reconstituted and diluted in sodium chloride solution 0.9% (normal saline) to a concentration of 1.1 mg/mL to 3.4 mg/mL; total volume should not exceed 500 mL. Only sodium chloride solution 0.9% (normal saline) should be used. Protect infusion bag from light. Administer the first infusion over 3 hours and observe patients during the infusion and for at least 30 minutes following the initial dose for signs or symptoms of infusion-related reactions. Subsequent infusions may be administered over 1 to 2 hours if prior infusions were tolerated, and patients should be observed during the infusion and for at least 30 minutes after infusion.

Prior to each infusion of sacituzumab govitecan-hziy, premedication for the prevention of infusion reactions and chemotherapy-induced nausea and vomiting is recommended.

- Premedicate with antipyretics, histamine receptor 1 and histamine receptor 2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.
- Premedicate with a two or three drug (preferred) combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a neurokinin 1 receptor antagonist, as well as other drugs as indicated).

Criteria for evaluation:

Efficacy:

Anti-tumor efficacy assessments include PFS, ORR, CBR, DOR and OS. Tumor response criteria will be based on RECIST v1.1. Myelosuppression endpoints will be based on reported hematology assessments, myelosuppression-related adverse event (AE) details, dose reductions/delays, and supportive care interventions (including transfusions).

Safety:

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

Statistical methods:

The following analysis populations are defined for the study.

Summary statistics will be provided for all endpoints. The categorical variables will be summarized by counts and percentages, the continuous variables will be summarized by mean, median, standard deviations, 25% and 75% percentiles, and minimum and maximum values.

Analysis population

The full analysis set (FAS) includes all enrolled patients who were administered at least 1 dose of study drug. Unless otherwise specified, the FAS is the primary analysis set for all efficacy analyses.

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

The safety population includes all enrolled patients who received at least 1 dose of study drug. All safety analyses will be evaluated using the safety population.

Statistical analysis methods for primary and secondary endpoints

Analysis for primary efficacy endpoint

The primary endpoint, PFS, is defined as the time (months) from the date of first dose of study drug until the date of documented radiographic disease progression (PD) per RECIST v1.1 or death due to any cause, whichever comes first. For patients who do not experience PD or are alive at the time of performing the analysis, PFS will be calculated per censoring rules detailed in the Statistical Analysis Plan. The primary analysis for PFS will be conducted at the time when 36 patients have radiographically-determined disease progression or have died. A Kaplan-Meier plot will be produced. The median, 25th percentile, and 75th percentile of PFS will be estimated using the Kaplan-Meier method with their corresponding 95% confidence internal (CI) calculated based on the method by Brookmeyer and Crowley (1982). PFS will be analyzed on the FAS population.

Analysis for secondary anti-tumor efficacy endpoints:

Tumor response:

Objective response rate is defined as the proportion of patients with best overall response (BOR) of either confirmed complete response (CR) or confirmed partial response (PR) per RECIST v1.1. ORR, along with its 95% two-sided CI using the Clopper-Pearson method, will be computed. ORR will be analyzed on the RE population.

CBR is defined as the proportion of patients with a BOR of confirmed CR, confirmed PR, or stable disease lasting 24 weeks or longer from the first date of study drug administration. CBR will be analyzed similarly as ORR based on the RE population.

DOR is the time (months) between the date of achieving first objective response (CR or PR), confirmed at the next tumor scan, and the date of documented disease progression per RECIST v1.1 or death, whichever comes first. Patients who do not experience objective CR or PR will not be included in the analysis. For patients with objective response who do not reach radiographically determined PD or die at the time of analysis, censored time will be calculated following the rules detailed in Section 12.4.6.2. The median, 25th percentile and 75th percentile will be estimated using the Kaplan-Meier method with their corresponding 95% CI calculated based on the method by Brookmeyer and Crowley (1982).

OS:

OS is defined as the time (months) from the date of first dose of study drug to the date of death for patients who died in the study due to any cause, and the time to the last contact date known to be

alive for those patients who survived as of the date for final database lock (censored cases). OS will be conducted at the time when approximately 70% of patients (~32 patients) have died. Kaplan-Meier plots will be produced. The median, 25th percentile, and 75th percentile of OS will be estimated using the Kaplan-Meier method with their corresponding 95% CI calculated based on the method by Brookmeyer and Crowley (1982). OS will be analyzed on the FAS.

Analysis for myelosuppression endpoints:

The myelosuppression endpoints include the occurrence of severe neutropenia (SN). SN is defined as the absolute neutrophil count (ANC) laboratory value that meets the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 criteria for ≥ Grade 4 toxicity (i.e., ANC < 0.5 x 10^9/L in SI Unit). The number and percentage of patients with at least one occurrence of SN during the treatment period will be summarized. For counting myelosuppression endpoints (e.g., the number of red blood cell [RBC] transfusions on/after Week 5, and the number of dose reductions during the treatment period), the total number of the event, the total duration of treatment period (either in the unit of weeks or cycles), and event rate per 100 weeks or cycles will be summarized. For example, the event rate for RBC transfusions on/after Week 5 will be reported per 100 weeks and that for dose reduction will be reported per 100 cycles. For a given event, patients without any events during the treatment period will be assigned a value 0 to be included in the analysis.

Analysis for safety endpoints

Safety and tolerability will be assessed by AEs, dose modifications, laboratory tests, vital signs, and ECG. Safety data will be summarized using descriptive statistics based on the safety population. AEs are defined as those events occurring or worsening after treatment has begun on this study. AE data will be coded to system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities. The severity (toxicity grades 1-5) of AEs will be graded by Investigators according to NCI-CTCAE Version 5.0. Any AE, AEs related to study drug (trilaciclib or sacituzumab govitecan-hziy), AEs leading to study drug discontinuation, dose modification, trilaciclib adverse events of special interest will be summarized by system organ class, preferred term, and CTCAE grade, as appropriate.

For laboratory assessments, vital signs, and ECG intervals, observed values and changes from baseline will be summarized. For chemistry and hematology laboratory parameters, clinical labs will be characterized according to CTCAE toxicity grade 1 to 5, v5.0 when possible, and the number and percentage of patients within each CTCAE grade will be summarized for the overall treatment period as well as for each cycle. Safety data collected through scheduled or unscheduled visits will all be included in the safety evaluation.

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

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3. LIST OF ABBREVIATIONS

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

Table 1: Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine or Cys-loop superfamily of ligand-gated ion channels
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BOR	best overall response
BRCA	breast cancer gene
BSA	body surface area
CAP	College of American Pathologists
CBC	complete blood count
CBR	clinical benefit rate
CD	cluster of differentiation
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CNS	central nervous system
CPS	combined positive score
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

Abbreviation	Definition
DNA	deoxyribonucleic acid
DOR	duration of objective response
DSN	duration of severe neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
E/P	etoposide plus carboplatin
E/P/A	etoposide plus carboplatin plus atezolizumab
ER	estrogen receptor
ESA	erythropoiesis stimulating agent
ES-SCLC	extensive-stage small cell lung cancer
FAS	full analysis set
FDA	Food and Drug Administration
FDG	[^{18}F]-fluorodeoxyglucose
FN	febrile neutropenia
FSH	follicle stimulating hormone
G_1	gap 1 phase of the cell cycle
G1T28	trilaciclib; formerly G1T28-1
GC	gemcitabine and carboplatin
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
H1/H2	histamine receptor 1/2
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
HSPC	hematopoietic stem and progenitor cell
IB	Investigator's Brochure
IC	tumor-infiltrating immune cells

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitors
ID	identification
IEC	independent ethics committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
INR	International Normalized Ratio
IRB	institutional review board
IV	intravenous
LFT	liver function test
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRI	magnetic resonance imaging
NaF	sodium fluoride
NCI	National Cancer Institute
NK1	neurokinin 1
OAT1 or 3	organic anion transporter 1 or 3
OATP1B1 or 1B3	organic anion transporting polypeptide 1B1 or 1B3
OCT1 or 2	organic cation transporter 1 or 2
ORR	objective response rate
OS	overall survival
PARP	poly adenosine diphosphate-ribose polymerase
PCS	potentially clinically significant
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PES	polyether sulfone

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PTFE	polytetrafluorethylene
PVG	pharmacovigilance
QTcF	QT corrected interval using Fridericia's formula
RBC	red blood cell
RE	Response Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SMC	Safety Monitoring Committee
SN	severe neutropenia
SUSAR	suspected unexpected serious adverse reactions
TCR	T cell receptor
TIL	tumor infiltrating lymphocyte
TNBC	triple-negative breast cancer
Trop-2	trophoblast cell surface antigen 2
ULN	upper limit of normal
US	United States

4. INTRODUCTION

4.1. Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) has been characterized by several aggressive clinicopathologic features, including onset at a younger age, large, high-grade tumors, and a propensity for visceral metastasis (Cheang, 2008; Foulkes, 2010). The estimated median survival from the time of diagnosis is approximately 13-18 months and the median age at diagnosis is approximately 50 years (Kassam, 2009; Yardley, 2018). Treatments which are effective for hormone receptor-positive breast cancer and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, such as endocrine therapy or HER2-targeted therapies (e.g., trastuzumab) are not effective in TNBC, which lacks these markers. In particular, chemotherapies that target deoxyribonucleic acid (DNA) repair (e.g., platinum compounds) and cell proliferation (e.g., taxanes and anthracyclines, like doxorubicin) have been found to be the most effective in TNBC; however, these treatments are limited by toxicity and eventually all patients develop drug resistance.

The combination of immune checkpoint inhibitors (ICIs) with chemotherapy have provided a meaningful step forward for the treatment of patients with programmed death-ligand 1 (PD-L1) positive locally advanced unresectable/metastatic TNBC, but due to the potential treatment toxicities associated with ICIs, not all patients with PD-L1 positive TNBC are appropriate candidates for ICI treatment and, as would be expected, the patient population with PD-L1 negative TNBC did not derive benefit. Additional available targeted therapies approved by the FDA are poly adenosine diphosphate-ribose polymerase (PARP) inhibitors such as olaparib for the treatment of patients with germline breast cancer gene (BRCA)-positive, HER2-negative metastatic breast cancer (MBC) who have previously received chemotherapy and talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer. While these two targeted therapies offer benefit to patients with TNBC, they are limited to those with germline BRCA mutations (~9-18% of TNBC patients; Hahnen, 2017). Although ICIs and PARP inhibitors have shown promising first-line benefits, single-agent chemotherapy remains the standard of care for previously treated (beyond first-line) metastatic TNBC (Bardia, 2021).

In 2020, accelerated approval was granted by FDA for sacituzumab govitecan-hziy (Trodelvy®) for the treatment of adult patients with metastatic TNBC who have received at least two prior therapies for metastatic disease. Sacituzumab govitecan-hziy is a trophoblast cell surface antigen 2 (Trop-2)-directed antibody-drug conjugate linked to SN-38, the active metabolite of irinotecan, a topoisomerase I inhibitor (for more information, refer to Section 6.5). The accelerated approval was based on results from the Phase 2 IMMU-132-01 trial where patients (N=108) treated with sacituzumab govitecan-hziy had an objective response rate (ORR) of 33.3%, median duration of response (DOR) of 7.7 months (95% CI: 4.9-10.8 months), and 55.5% and 16.7% of patients having a DOR of ≥6 months and ≥12 months, respectively (Bardia, 2019). In 2021, full approval was granted by FDA based on the results from the Phase 3 ASCENT trial (Bardia, 2021). Median PFS for patients receiving sacituzumab govitecan-hziy was 4.8 months (95% CI: 4.1-5.8 months) compared with 1.7 months (95% CI:1.5-2.5 months) in those receiving physician's choice of single-agent chemotherapy (hazard ration [HR] 0.43, 95% CI: 0.35-0.54, P< 0.0001) and median overall survival (OS) was 11.8 months (95% CI: 10.5-13.8 months) and

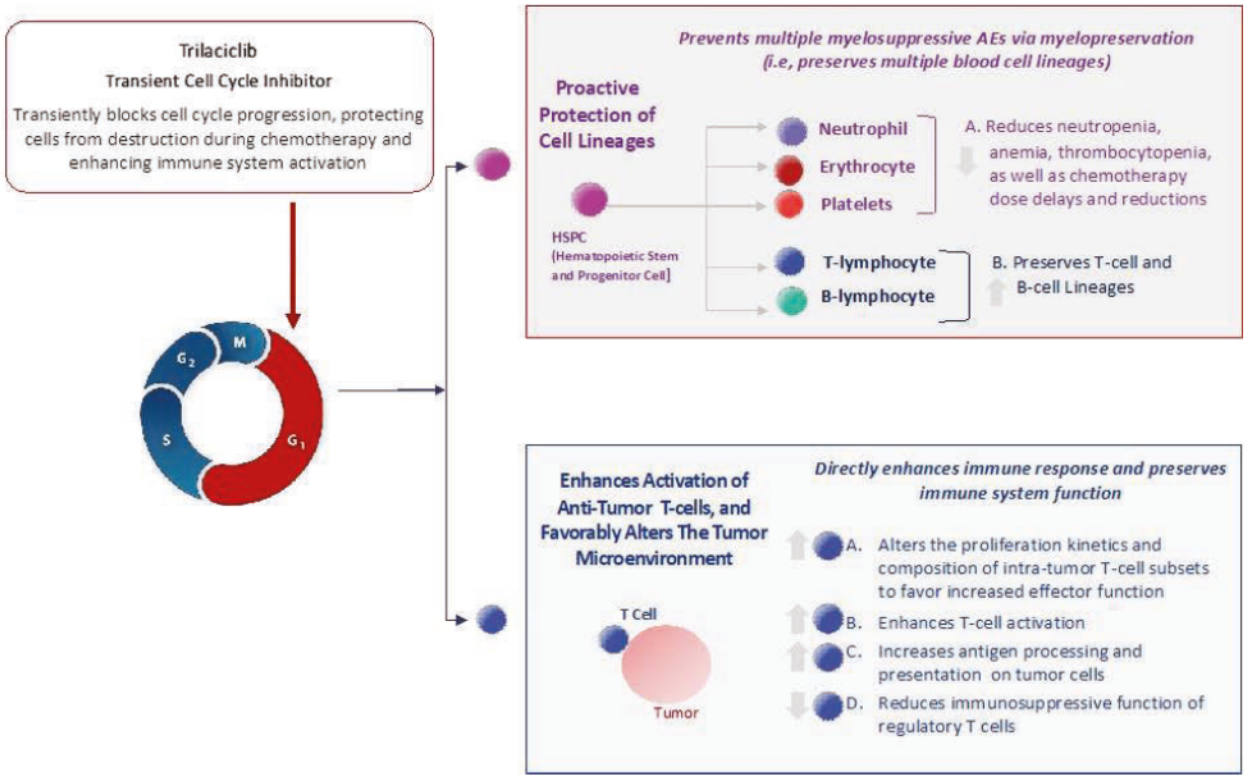
6.9 months (95% CI: 5.9-7.6 months), respectively (HR 0.51, 95% CI: 0.41-0.62, P< 0.0001) (Trodelvy Package Insert, 2021). In that same study, in a subset of patients without brain metastasis at baseline (88% of the full study population), median PFS for patients receiving sacituzumab govitecan-hziy was 5.6 months (95% CI: 4.3-6.3 months) compared with 1.7 months (95% CI: 1.5-2.5 months) in those receiving physician's choice of single-agent chemotherapy (HR 0.41, 95% CI: 0.32-0.52, P<0.001) and median OS was 12.1 months (95% CI: 10.7-14.0 months) and 6.7 months (5.8-7.7 months), respectively (HR 0.48, 95% CI: 0.38-0.59, P<0.001) (Bardia, 2021).

Overall, patients with TNBC have few treatment options beyond standard chemotherapy. Even though there are now available targeted therapies for TNBC, these therapies are limited to those eligible patients expressing PD-L1-positive disease (ICIs) and/or those that carry a germline BRCA mutation (PARP inhibitors) and in the case of ICIs, come with additional toxicity. In addition to these limitations, chemotherapy-induced immunosuppression may also affect anti-tumor efficacy due to an inability of the host immune system to effectively mount a response against the cancer. Therefore, preserving the bone marrow and immune system from the cytotoxic effects of chemotherapy has the potential to maximize the anti-tumor activity of the chemotherapy while minimizing myelotoxicity. Novel therapeutic options that can offer similar or improved antitumor efficacy without the associated high-grade toxicities are clearly needed for all TNBC patients, regardless of PD-L1 or BRCA status.

4.2. Study Rationale

Trilaciclib is a highly potent and selective, reversible, cyclin-dependent kinase (CDK) 4/6 inhibitor that preserves hematopoietic stem and progenitor cells (HSPCs) as well as immune system function during chemotherapy (myeloprotection) in addition to directly enhancing anti-tumor immunity (anti-cancer efficacy) (Figure 1). Both HSPC and lymphocyte proliferation are dependent on CDK4/6 activity (Kozar, 2004; Malumbres, 2004; Ramsey, 2007; Horsley, 2008) and become arrested in the gap 1 (G_1) phase of the cell cycle upon exposure to trilaciclib (He, 2017). This trilaciclib-induced transient cell cycle arrest has been demonstrated to provide resistance to chemotherapy-induced cell damage by preventing HSPCs from proliferating in the presence of cytotoxic chemotherapy and favorably altering the tumor immune microenvironment through transient T cell inhibition when combined with chemotherapy (He, 2017; Bisi, 2016; Lai, 2018; Sorrentino, 2017). In February 2021, the FDA approved trilaciclib (COSELA™) as a treatment to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

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



4.2.1. Rationale for Improving Anti-tumor Efficacy with Trilaciclib

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

The G1T28-04 study was the first evaluation of trilaciclib in a tumor type other than SCLC where trilaciclib development focused on myeloprotection benefits (Section 4.3.2.1). Three randomized, double-blind, Phase 2 clinical trials evaluating trilaciclib/placebo administered prior to chemotherapy in patients with SCLC have demonstrated in a variety of clinical settings (first-, second-, third-line SCLC treated with several different classes of chemotherapy) that trilaciclib can prevent chemotherapy-induced myelosuppression as measured by multiple endpoints (Weiss, 2019; Hart, 2021; Daniel, 2019). In addition, these myeloprotection benefits were observed in the setting of minor improvements in PFS and OS as evidenced by HRs <1.0 in

almost all clinical settings for trilaciclib compared with placebo. For more detailed information, refer to the trilaciclib Investigator's Brochure (IB).

In contrast to the previously observed SCLC results, the addition of trilaciclib to chemotherapy for patients with TNBC in G1T28-04 did not result in statistically significant improvements in myelosuppression endpoints but instead resulted in a substantial improvement in anti-tumor efficacy as measured by OS (median OS duration in control 12.6 months vs. not evaluable or 17.8 months in the two trilaciclib groups, HR 0.31 [95% CI: 0.15-0.63] and HR 0.40 [95% CI: 0.22-0.74], respectively) and by PFS (median PFS in control 5.7 months vs. 9.4 months or 7.3 months in the two trilaciclib groups HR 0.62 [95% CI: 0.32-1.20] and 0.63 [95% CI: 0.32-1.22], respectively and ORR (29.2% in the control group vs. 50.0% and 38.7% in the two trilaciclib groups, respectively; not statistically significant) (Tan, 2019; O'Shaughnessy, 2020). The clinically meaningful anti-tumor efficacy results observed in G1T28-04 were noted across both of the trilaciclib treatment groups and in patients with both PD-L1 positive and negative tumors, and these benefits were observed for multiple anti-tumor efficacy endpoints, with ORR, PFS, and OS endpoints all showing numerical improvement with the addition of trilaciclib to GC compared with GC alone. These results were observed in the context of a control group that is reflective of published literature for this patient population (refer to Section 4.3.2.1 for additional information). A confirmatory Phase 3 study is currently ongoing (Study G1T28-208, NCT04799249).

The differences between the observed anti-tumor efficacy results in the SCLC trials and those in the TNBC trial are hypothesized to result from differences in the key variables between the two clinical situations. Unlike chemotherapy-induced myelosuppression, the effects of trilaciclib on anti-tumor efficacy are predicted to be primarily driven by the tumor type, chemotherapy type, and host, i.e., (1) the tumor type must be sufficiently responsive to chemotherapy such that maintenance of chemotherapy dose intensity is beneficial, (2) the tumor must be sufficiently immunogenic and sensitive to the host cytolytic efforts as to see improvement in anti-tumor endpoints like OS, (3) the chemotherapy should promote immune activation, (4) the host must be able to tolerate the standard of care chemotherapy dose intensity, and (5) the host must be able to mount an effective cytolytic response against the tumor. In the SCLC trials, the addition of trilaciclib to the standard of care therapies provided modest improvement, to neutral effects, on measures of anti-tumor efficacy including ORR, PFS, and OS. These results are not surprising considering that SCLC is one of the most aggressive solid tumors, relapses quickly after completion of chemotherapy, has been shown to be relatively insensitive to multiple attempts to intensify the chemotherapy regimen beyond the current standard of care, and is not particularly immunogenic or sensitive to immune modulation. In contrast, TNBC has been shown to be immunogenic and more sensitive to immune modulation compared to SCLC (Semenova, 2015; He, 2017; Carvajal-Hausdorf, 2019; Liu, 2018).

In addition, the G1T28-04 results were generally consistent across patient subgroups, including CDK4/6 status. Patient tumors were characterized as CDK4/6 independent, dependent, or indeterminate using two established signatures (Prosigna Breast Cancer Prognostic Gene Signature Assay [PAM50] and Lehmann triple-negative breast cancer type) (Prat, 2014; Lehmann, 2016; Asghar, 2017). As expected, these data suggest trilaciclib does not antagonize chemotherapy efficacy regardless of CDK4/6 status, including tumors that are CDK4/6 indeterminate or dependent (Tan, 2019; O'Shaughnessy, 2020). These data are consistent that TNBC is predominantly CDK4/6 independent and therefore not sensitive to CDK4/6 inhibition.

The combination of trilaciclib plus sacituzumab govitecan-hziy in patients with TNBC is predicted to demonstrate improvement in anti-tumor efficacy similar to the results observed in Study G1T28-04. As noted above, TNBC has been shown to be immunogenic and more sensitive to immune modulation and sacituzumab govitecan-hziy induces DNA damage leading to apoptosis and cell death through uptake of tumor cells (see Section 6.5). This mechanism of action compliments trilaciclib's positive impact on anti-tumor immune modulation (see Section 4.2.2). Therefore, the combination of trilaciclib plus sacituzumab govitecan-hziy in patients with TNBC fulfills the key variables described above that are indicative of an improvement in anti-tumor efficacy.

4.2.2. Rationale for Immune Mechanism of Trilaciclib

In the G1T28-05 study evaluating trilaciclib prior to cisplatin, etoposide, and atezolizumab (E/P/A) in patients with extensive stage SCLC, flow cytometry and T cell receptor (TCR) immunosequencing data revealed that patients receiving trilaciclib had an increased ratio of total and activated cluster of differentiation (CD)8^+ T cells to Tregs and increased peripheral T cell clonal expansion suggesting enhanced T cell activation. Furthermore, there was significant enhancement in newly detected expanded clones among patients receiving trilaciclib compared with placebo, which was stronger among patients with an anti-tumor response to etoposide plus carboplatin plus atezolizumab (E/P/A), suggesting that trilaciclib may enhance tumor antigen presentation, a phenomenon that has been observed in preclinical studies with other CDK4/6 inhibitors (Daniel, 2020).

These observations are consistent with those from the G1T28-02 Phase 2 study of patients with extensive stage SCLC receiving trilaciclib prior to etoposide plus carboplatin (E/P). In G1T28-02, a higher proportion of activated or effector $CD8^+$ and $CD4^+$ T cells was observed in patients receiving trilaciclib compared with placebo. In addition, high levels of T cell clonal expansion were associated with improved PFS and numerically longer median OS. Taken together, the data suggest that the addition of trilaciclib at least preserves, if not enhances, T cell function during treatment with E/P or E/P/A (Lai, 2020).

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

Despite the compelling clinical efficacy of ICIs, the majority of patients eventually develop therapeutic resistance leading to disease progression after an initial response. Mechanisms of ICI resistance include genetic, epigenetic, and cellular signaling alterations that dysregulate neoantigen presentation/processing and disrupt cytotoxic T cells activity as well as mechanisms in which non-cancerous stromal or immune cells promote growth and resistance to ICIs (Liu, 2018; Barrueto, 2020; Jenkins, 2018; Fares, 2019; Borcherding, 2018; Gide, 2018). Interestingly, many of the mechanisms to overcome ICI-induced resistance have been associated with the

immune activating effects of CDK4/6 inhibition, including increasing antigen presentation (major histocompatibility complex class I), enhancing T cell clonality and tumor infiltration, inhibiting regulatory T cell proliferation, decreasing T cell exhaustion markers (programmed cell death protein 1 [PD-1], cytotoxic T-lymphocyte associated protein 4, and T cell immunoglobulin and mucin domain 3), stabilizing expression of PD-L1 on tumor cells, promoting dendritic cell migration, and increasing T effector cell function through high interferon (IFN) gamma production. These data suggest patients may benefit from trilaciclib after progressing on ICI treatment (Chaikovsky and Sage, 2018; Deng, 2018; Goel, 2017; Schaer, 2018; Lai, 2020; Bonelli, 2019; Teh and Aplin, 2019).

Taken together, these data from clinical trials evaluating trilaciclib in a variety of clinical contexts suggest that trilaciclib has a consistent positive impact on anti-tumor immune modulation. Furthermore, there appears to be several immune-based mechanisms through which this effect can be mediated including neoantigen presentation and T cell activation and function. Therefore, it is possible that trilaciclib may improve anti-tumor outcomes, such as PFS and OS, in TNBC patients treated with sacituzumab govitecan-hziy.

4.2.3. Rationale for Myeloprotection

Trilaciclib has shown well-documented improvement in myelosuppression outcomes that could provide benefit to patients receiving sacituzumab govitecan-hziy. In the Phase 3 ASCENT trial, 52% of patients with TNBC treated with sacituzumab govitecan-hziy experienced Grade 3/4 neutropenia (14% Grade 4) with 6% experiencing febrile neutropenia. In ASCENT, the median time to onset of the first event of Grade ≥3 neutropenia in patients treated with sacituzumab govitecan-hziy was 21 days (Rugo, 2020). In addition, 9% of patients treated with sacituzumab govitecan-hziy experienced Grade 3/4 anemia (Bardia, 2021; Trodelvy Package Insert, 2021). Patients treated for SCLC with trilaciclib had marked reductions in the occurrence of these outcomes (Table 2), requiring less supportive care and experienced enhanced quality of life. The exploratory patient-reported outcome endpoints in these patients suggested that trilaciclib administered prior to chemotherapy may offer potential benefit in multiple aspects of health-related quality of life with a greater magnitude of effect observed for fatigue and anemia symptoms and functional limitations (Weiss, 2019). An analysis of integrated fatigue subscale data from Functional Assessment of Cancer Therapy – Anemia in the three studies showed that trilaciclib delayed the median time to deterioration by approximately 5 months for fatigue (7.03 months in the trilaciclib group vs. 2.33 months in the placebo group, HR 0.56, 95% CI: 0.37, 0.85) (Weiss, 2021). For more detailed information, refer to the trilaciclib IB. Given that the rate of Grade 3/4 neutropenia in TNBC patients treated with sacituzumab govitecan-hziy is higher than that observed in TNBC patients from Study G1T28-04 treated with gemcitabine/carboplatin (52% vs. 26.5%), it is possible that the myeloprotective benefits of trilaciclib may also be observed in TNBC patients treated with sacituzumab govitecan-hziy.

Table 2: Integrated Analysis for Myeloprotection Efficacy in SCLC (Studies G1T28-02, G1T28-03, and G1T28-05)

	Placebo + Chemo	Trilaciclib + Chemo	2-sided p-value
ITT Set	119	123	
Neutrophils			
DSN [days] in Cycle 1 – Mean (SD)[a]	4 (5.1)	0 (1.8)	<0.0001
Occurrence of SN (Yes, %)[b]	64 (52.9)	14 (11.4)	<0.0001
RBCs			
Occurrence of Grade 3/4 hemoglobin decreased (anemia) (Yes, %)[b]	38 (31.9)	25 (20.3)	0.0279
Occurrence of RBC transfusion on/after 5 weeks (Yes, %)[b]	31 (26.1)	18 (14.6)	0.0252
Cumulative incidence of RBC transfusion on/after 5 weeks - Event rate (per 100 weeks)[c]	3.1	1.5	0.0027
Platelets			
Occurrence of Grade 3/4 platelet count decreased (thrombocytopenia) (Yes, %)[b]	43 (36.1)	24 (19.5)	0.0067
Occurrence of platelet transfusion (Yes, %)[b]	11 (9.2)	10 (8.1)	0.9564
Cumulative incidence of platelet transfusion – Event rate (per 100 weeks)[c]	1.7	1.1	0.5169

ANC=absolute neutrophil count; Chemo=chemotherapy; DSN=duration of severe (Grade 4) neutropenia; ECOG=Eastern Cooperative Group; RBC=red blood cells; SCLC=small cell lung cancer; SD=standard deviation; SN=severe (Grade 4) neutropenia which is defined as ANC < 500/mm^3; ITT=intent to treat.
Chemo=etoposide + platinum in G1T28-02, etoposide + platinum + atezolizumab in G1T28-05, and topotecan in G1T28-03. Standard supportive care interventions were allowed for all arms.
[a] p-value was obtained from a nonparametric analysis of covariance (ANCOVA).
[b] p-value was obtained from a modified Poisson model.
[c] p-value was obtained from a negative binomial model. All three models contained fixed effect of treatment, ECOG performance status (0-1 versus 2), Presence of brain metastases (Y/N), and study (G1T28-02, G1T28-03, or G1T28-05). Corresponding baseline assessment was also included as a covariate.

4.3. Background

In February 2021, the US FDA approved trilaciclib (COSELA™) as a treatment to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC.

4.3.1. Summary of Nonclinical Data

A summary of the trilaciclib nonclinical data is presented in the trilaciclib IB.

Nonclinical data related to sacituzumab govitecan-hziy are provided in the local prescribing information.

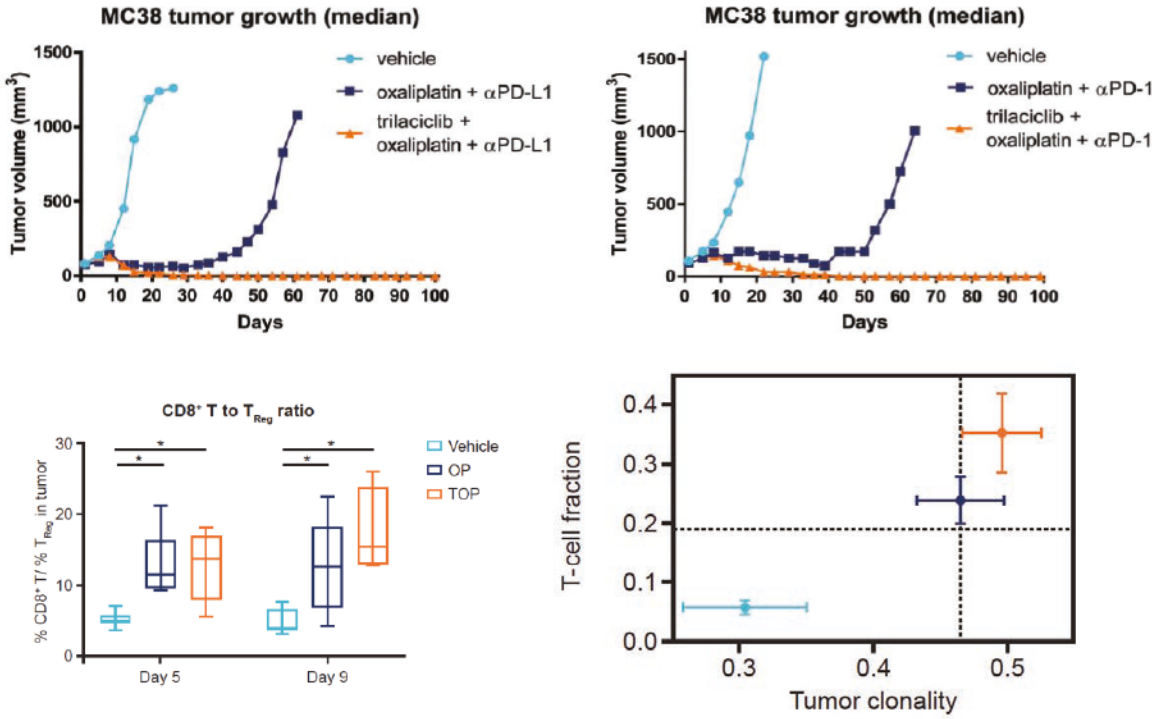
4.3.1.1. Pharmacology Studies

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

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

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

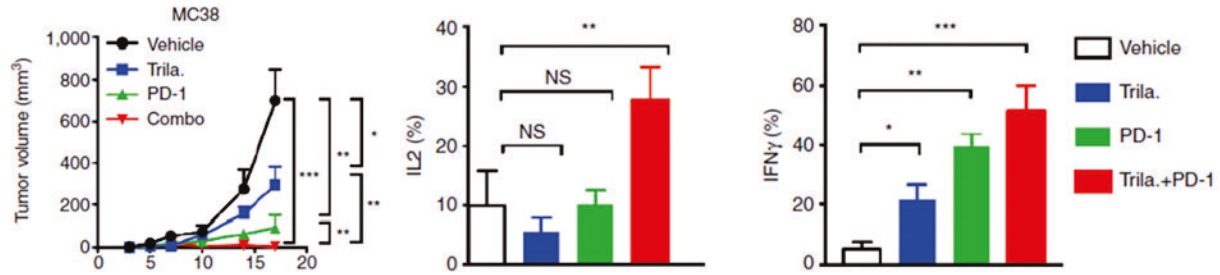
Figure 2: The Addition of Trilaciclib to Chemotherapy/Immune Checkpoint Inhibitor Treatment Enhances Efficacy Through T Cell Activation



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

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

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



CD=cluster of differentiation; IFN=interferon; IL=interleukin; PD-1=programmed cell death protein 1; NS=not significant

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

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

4.3.1.2. Pharmacokinetic Studies

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

In vitro analyses of direct and time-dependent inhibition suggest that drug interactions based on inhibition of cytochrome P450 (CYP)1A2-, 2B6-, 2C8-, 2C9-, 2C19-, and 2D6-mediated metabolic pathways are unlikely at clinical doses; however, the studies do suggest that drug-drug interactions (DDI) based on trilaciclib-mediated inhibition of CYP3A4-mediated metabolic pathways are possible (see Section 4.3.2.1.1 for additional details). Additionally, in vitro induction studies of the 3 major inducible CYP enzymes (CYP1A2, CYP3A4, and CYP2B6) in human hepatocytes suggest that trilaciclib-mediated induction is unlikely.

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

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

However, in vitro, trilaciclib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1), multidrug and toxin extrusion 2-K (MATE2-K), organic cation transporter 1 (OCT1), and organic cation transporter 2 (OCT2) (see Section 4.3.2.1.1 for additional details).

4.3.2. Summary of Clinical Data

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

4.3.2.1. Efficacy

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

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

At the US FDA approved dose of 240 mg/m^2, across all three SCLC studies, trilaciclib administered prior to chemotherapy statistically significantly reduced the duration of severe neutropenia (DSN) in Cycle 1 and occurrence of severe neutropenia (SN) (primary endpoints) compared with placebo. An integrated data analysis of the three SCLC studies (G1T28-02, G1T28-03, and G1T28-05) for 8 of the most relevant myelosuppression endpoints (neutrophils, red blood cells [RBCs] and platelets) demonstrated statistically significant, and clinically meaningful, improvements for trilaciclib over available therapies in 6 of 8 endpoints across multiple lineages. Importantly, these myeloprotection benefits come with an overall improved safety profile compared with available therapy, as evidenced by reduced high grade treatment-emergent adverse events (AEs) across all SCLC studies, and no detriment to

anti-tumor efficacy results. For a more detailed description of the results, refer to the trilaciclib IB.

Results from the TNBC Study G1T28-04 demonstrated that although the addition of trilaciclib at the US FDA approved dose of 240 mg/m^2 to GC did not statistically significantly improve chemotherapy-induced myelosuppression as measured by the neutrophil-based endpoints of DSN in Cycle 1 and occurrence of SN, there were trends toward improvement in RBC and platelet-based measures. In addition, anti-tumor efficacy results demonstrated a clinically meaningful improvement in PFS and OS (Figure 4; Table 3). This meaningful anti-tumor efficacy was observed across multiple subgroups, including both PD-L1 positive and negative tumor types (Table 4), and in both trilaciclib groups compared with the control group.

As mentioned in Section 4.3.1.1, there is a hypothetical risk that administration of trilaciclib prior to chemotherapy could decrease chemotherapy efficacy. This hypothetical risk is countered by the results observed in Study G1T28-04 which suggested that the addition of trilaciclib improves the anti-tumor efficacy of GC regardless of the CDK4/6 status of the TNBC tumor. Although TNBC tumors are predominantly classified as CDK4/6 independent (i.e., their replication is not sensitive to CDK4/6 inhibition), there is a small subset of patients whose tumors are classified as either CDK4/6 indeterminate or CDK4/6 dependent. When the TNBC population enrolled in Study G1T28-04 is divided into these subsets, evaluation of the anti-tumor efficacy in patients whose tumors are classified as CDK4/6 indeterminate or CDK4/6 dependent suggests that trilaciclib does not antagonize the anti-tumor effects of GC. Specifically, PFS and OS did not decrease when trilaciclib was added to GC in the most CDK4/6-dependent population (see trilaciclib IB).

Table 3: G1T28-04: Summary of Overall Survival and Progression-Free Survival (ITT Analysis Set)

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

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

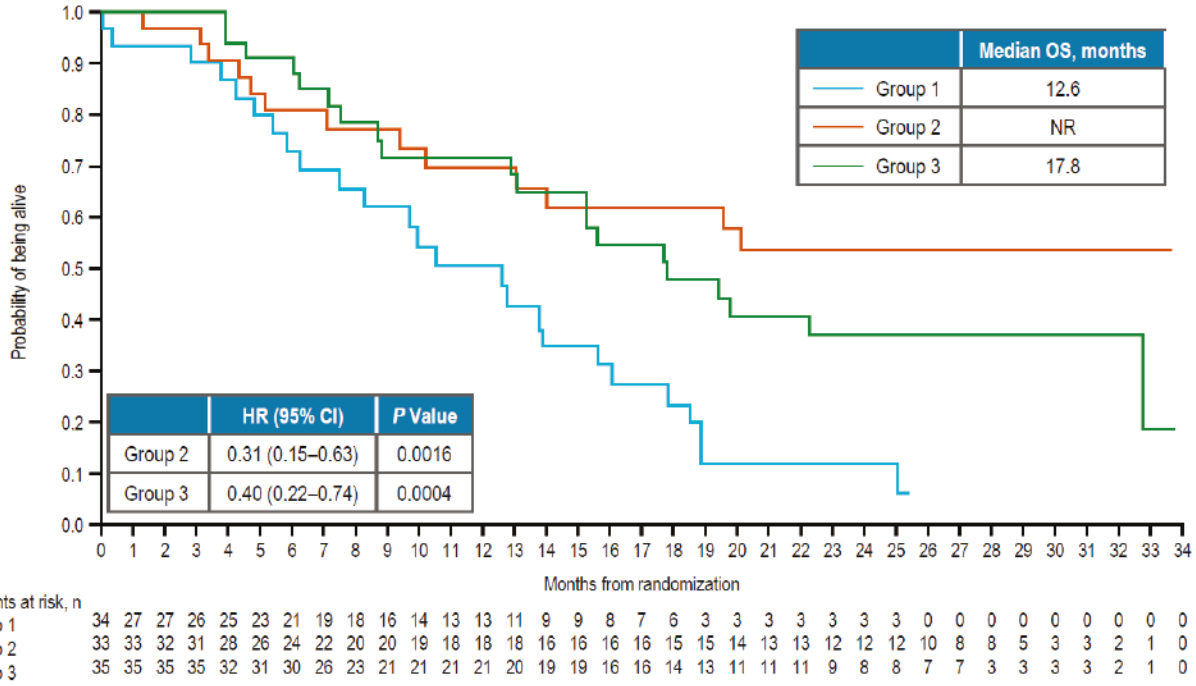
[a] Calculated using the Kaplan-Meier method

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

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

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

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



CI=confidence interval; GC=gemcitabine and carboplatin; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; OS=overall survival.

Group 1: GC administered on Days 1 and 8 of 21-day cycles; Group 2: Trilaciclib and GC administered on Days 1 and 8 of 21-day cycles; Group 3: Trilaciclib administered on Days 1, 2, 8, and 9 and GC administered on Days 1 and 8 of 21-day cycles.

Note: The HR and its 95% CI comparing Group 1 and 2 and Group 1 and 3 were calculated using the Cox regression model with treatment and stratification factors of number of prior lines of therapy (0 versus 1 or 2) and liver involvement.

Note: P-values comparing Group 1 and 2 and Group 1 and 3 were calculated using the stratified log-rank test to account for the number of prior lines of therapy (0 versus 1 or 2) and liver involvement as the stratification factors.

Note: data generated from final database.

Table 4: G1T28-04: Tumor Response According to PD-L1 Status

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

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

4.3.2.1.1. Pharmacokinetics

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

In an additional clinical DDI assessment in healthy subjects, trilaciclib increased metformin (MATE1, MATE2-K and OCT2 substrate) exposure by 65% compared with administration of metformin alone. However, due to the intermittent schedule of trilaciclib administration and the observation that the effect of trilaciclib on metformin was similar to mild to moderate reductions in renal function, the clinical significance of the metformin plasma concentration increase is not expected to be high.

Co-administration of trilaciclib may increase the concentration or net accumulation of OCT2, MATE1, and MATE-2K substrates in the kidney (e.g., dofetilide and dalfampridine).

4.3.3. Risks

4.3.3.1. Trilaciclib

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

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

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

Adverse events of special interest (AESIs) identified for trilaciclib in the integrated safety summary are described below. Some AESIs have been infrequently reported (or not reported) in the trilaciclib clinical program to date but are considered to be potential class effects of CDK4/6

inhibitors. However, as trilaciclib is given IV and only when chemotherapy is administered, the safety profile of trilaciclib appears to be different from that of the oral, chronically-dosed members of its pharmacologic class. All patients will be monitored for these events and dose modification and discontinuation guidelines are provided in Section 9.3.

Trilaciclib AESIs:

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

   Monitor patients for signs and symptoms of injection-site reactions, phlebitis, and thrombophlebitis, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue trilaciclib.

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

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

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

   Monitor patients for pulmonary symptoms indicative of interstitial lung disease/pneumonitis such as cough, dyspnea, and hypoxia. For recurrent moderate

(Grade 2) interstitial lung disease/pneumonitis, permanently discontinue trilaciclib. For severe (Grade 3) or life-threatening (Grade 4) interstitial lung disease/pneumonitis, permanently discontinue trilaciclib.

4. **Hepatotoxicity:** Both nonclinical toxicology studies with trilaciclib, and clinical studies with other compounds with a similar MOA, report reversible elevations in transaminases with continuous dosing. There has been only 1 instance of Grade 4 alanine aminotransferase (ALT) increase in a patient receiving trilaciclib, no Grade 4 aspartate aminotransferase (AST) increases, and no cases of Hy's law reported in patients receiving trilaciclib. However, generally low grade and transient increases in AST, ALT, or bilirubin have been observed in a small number of patients (~5%) receiving trilaciclib prior to chemotherapy. Patients with mild hepatic impairment have been treated with trilaciclib without a clinically significant increase in exposure or the frequency/severity of AEs.
5. **Embolic and Thrombotic Events, Venous:** The CDK4/6 inhibitor abemaciclib has been associated with an increased risk for venous thromboembolism when combined with endocrine therapy in patients with breast cancer. This same risk has not been reported for the other approved oral CDK4/6 inhibitors (ribociclib and palbociclib); therefore, it is not clear if this is a class effect. Approximately 3% of cancer patients that received trilaciclib prior to chemotherapy experienced a venous thromboembolic event and half of those events (3/6) were Grade 3 or 4. No Grade 5 events were reported. Approximately 2% of patients receiving chemotherapy alone or with placebo reported an embolic or thrombotic event, 1 of 3 such events was Grade 3.

4.3.3.2. Sacituzumab govitecan-hziy

Per Warnings and Precautions in the prescribing information for sacituzumab govitecan-hziy (Trodelvy Package Insert, 2021), the following are important risks related to sacituzumab govitecan-hziy use:

- Severe or life-threatening neutropenia (boxed warning)
- Severe diarrhea (boxed warning)
- Hypersensitivity and infusion-related reactions, including severe anaphylactic reactions
- Nausea and vomiting
- Patients with Reduced UGT1A1 Activity: Individuals who are homozygous for the *uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28* allele are at increased risk for neutropenia, febrile neutropenia, and anemia
- Embryo-fetal toxicity

4.4. Benefit/Risk Assessment

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

anti-tumor efficacy due to an inability of the host immune system to effectively mount a response against the cancer. Therefore, administration of trilaciclib to preserve the bone marrow and the immune system from the cytotoxic effects of chemotherapy has the potential to maximize anti-tumor activity of the chemotherapy. As stated in Section 4.3.2, the FDA approved dose of 240 mg/m^2 trilaciclib established in Phase 1b/2a SCLC studies and in the Phase 2 TNBC study will be used in this study and administered prior to the FDA approved dose for sacituzumab govitecan-hziy in TNBC.

Studies to date with trilaciclib have demonstrated a manageable safety profile (see Section 4.3.3.1). In Study G1T28-04, the rates of overall toxicity were comparable in TNBC patients who received trilaciclib with GC versus GC alone despite the 1.5-fold increase in the median number of cycles and 50% increase in the cumulative dose of both gemcitabine and carboplatin in patients who received trilaciclib. Rates of discontinuation due to an AE were not different between the trilaciclib groups and the GC alone group. Similarly, in patients with SCLC administered trilaciclib with E/P/A in Study G1T28-05, the rates of overall toxicity profile were comparable in patients who received trilaciclib plus E/P/A versus placebo plus E/P/A despite the lower relative dose intensity of E/P/A being lower in patients in the placebo group compared with the trilaciclib group, with the trilaciclib group having a lower number of dose delays/reduction. In addition, patients receiving trilaciclib had lower rates of discontinuation due to an AE and atezolizumab AESIs as compared with patients receiving placebo. Finally, trilaciclib is currently being investigated in combination with irinotecan as part of a FOLFOXIRI/bevacizumab treatment regimen in patients with metastatic colorectal cancer (Study G1T28-207, NCT04607668). No new safety signals have been identified to date and there are no known risks of potential DDI between trilaciclib and SN-38.

In conclusion, the combination treatment of trilaciclib with sacituzumab govitecan-hziy offers the potential for clinical benefit with a favorable safety profile.

5. OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives of this study, and their associated endpoints, for patients who received at least 2 prior treatments, at least 1 in the metastatic setting for unresectable, locally advanced or metastatic TNBC being administered trilaciclib with sacituzumab govitecan-hziy, are presented in Table 5.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To evaluate the anti-tumor activity of trilaciclib when administered prior to sacituzumab govitecan-hziy	• PFS defined as time from the date of first dose of study drug to radiographic disease progression using RECIST v1.1 or death due to any cause, whichever occurs first; for patients without disease progression or death, PFS will be calculated per censoring rules.
Secondary Objective: Efficacy	
• To evaluate the anti-tumor activity of trilaciclib when administered prior to sacituzumab govitecan-hziy	• ORR defined as the percentage of patients with BOR of confirmed CR or confirmed PR per RECIST v1.1 • CBR defined as the percentage of patients with a BOR of confirmed CR, confirmed PR, or SD lasting 24 weeks or longer since the first date of study drug administration per RECIST v1.1 • DOR defined as duration of objective response • OS defined as time from the date of first dose of study drug to death due to any cause for those who died; or time to last contact known as alive for those who survived in the study (censored cases)
Secondary Objective: To evaluate the myeloprotective effects of trilaciclib	
• To evaluate the myeloprotective effects of trilaciclib when administered prior to sacituzumab govitecan-hziy	• Occurrence of SN (during Cycles 1/2 and overall study) • Occurrence of febrile neutropenia • Occurrence of G-CSF administration • Occurrence of Grade 3/4 decrease of hemoglobin • Occurrence and number of RBC transfusions on/after Week 5 • Occurrence of ESA administration • Occurrence of Grade 3/4 decrease of platelets • Occurrence and number of platelet transfusions • Occurrence of serious infections • Use of IV antibiotics

Objectives	Endpoints
Secondary Safety Objectives	
• To evaluate the safety and tolerability of trilaciclib when administered prior to sacituzumab govitecan-hziy	• Occurrence and severity of AEs by NCI CTCAE v5.0 • Trilaciclib AESIs • Changes in laboratory parameters (hematology and chemistry), vital signs and ECG parameters • Grade 3 or 4 abnormalities in chemistry laboratory parameters • Trilaciclib infusion interruptions • Sacituzumab govitecan-hziy infusion interruptions • Sacituzumab govitecan-hziy dose reduction and cycle delay

AE=adverse event; AESI=adverse event of special interest; BOR=best overall response; CBR=clinical benefit rate; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; DOR=duration of response; ECG=electrocardiogram; ESA=erythropoiesis stimulating agent; G-CSF=granulocyte colony-stimulating factor; IV=intravenous; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; SN=severe neutropenia

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an exploratory Phase 2, multicenter, open-label study evaluating the safety and efficacy of trilaciclib administered with sacituzumab govitecan-hziy in patients with unresectable locally advanced or metastatic TNBC who received at least 2 prior treatments, at least 1 in the metastatic setting. Inclusion/exclusion criteria are outlined in Section 7.1 and Section 7.2, respectively.

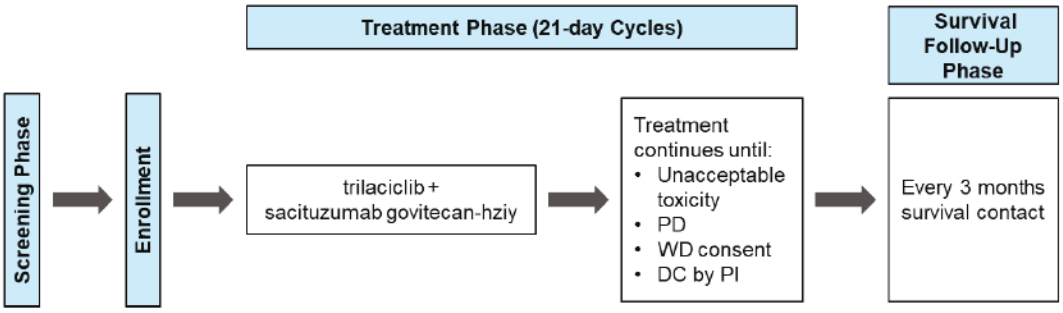
Approximately 45 patients will be enrolled.

Trilaciclib plus sacituzumab govitecan-hziy will be administered IV in 21-day cycles as follows:

- Trilaciclib 240 mg/m^2 administered as a 30-minute IV infusion completed within 4 hours prior to the start of sacituzumab govitecan-hziy on Day 1 and Day 8 of each 21-day treatment cycle.
- Sacituzumab govitecan-hziy 10 mg/kg administered IV on Day 1 and Day 8 of each 21-day treatment cycle. Administer the first infusion over 3 hours and observe patients during the infusion and for at least 30 minutes following the initial dose for signs or symptoms of infusion-related reactions. Subsequent infusions may be administered over 1 to 2 hours if prior infusions were tolerated, and patients should be observed during the infusion and for at least 30 minutes after infusion. Prior to each infusion of sacituzumab govitecan-hziy, premedication for the prevention of infusion reactions and chemotherapy-induced nausea and vomiting (CINV) is recommended.
  - Premedicate with antipyretics, histamine receptor 1 (H1) and histamine receptor 2 (H2) blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.
  - Premedicate with a two or three drug (preferred) combination regimen (e.g., dexamethasone with either a 5-hydroxytryptamine (5-HT3) receptor antagonist or a neurokinin 1 (NK1) receptor antagonist, as well as other drugs as indicated).

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

Figure 5: Study Schema



DC=dicontinued; PD=progressive disease; PI=Principal Investigator; WD=withdraw

Patients enrolled in the study will be eligible to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever comes first. Treatment cycles will occur consecutively without interruption, except when necessary, to manage toxicities or for administrative reasons. There should be no more than a 3-week delay from the next scheduled dose of sacituzumab govitecan-hziy. A dosing delay >3 weeks from the next scheduled dose may be permitted on a case-by-case basis with the approval of the Investigator and Medical Monitor.

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

An End of Treatment Visit will occur approximately 14 days following a patient's last dose of study treatment. Safety Follow-up visits (which may be a phone call) will occur 30 days after the last dose of study treatment. Patients will be followed for survival approximately every 3 months after the End of Treatment Visit. Survival Follow-up Visits may be done via telephone, email, or clinic visit. Unless otherwise decided by the Sponsor, the study will continue until approximately 70% of patients enrolled in the study have died.

A Safety Monitoring Committee (SMC) will monitor accumulating safety and disposition data with the first meeting planned when approximately 10 patients have completed at least 2 cycles of study treatment. The meetings will continue when approximately 25 enrolled patients have completed at least 2 cycles of study treatment and again when all enrolled patients have completed at least 2 cycles of study treatment or as defined in the SMC charter. Additional reviews may occur. For more information, refer to Section 11.4.

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

6.2. Rationale for Primary and Secondary Endpoints

6.2.1. Anti-tumor Efficacy

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

6.2.2. Myeloprotection

Patients experiencing chemotherapy-induced myelosuppression often face severe clinical consequences (e.g., febrile neutropenia [FN] predisposes patients to serious infections and even death). For those patients with neutropenia requiring hospitalization, the estimated inpatient mortality rates ranged from 3.4% to 10.5% depending on tumor type in 1 study, with an overall mortality rate of 6.8% (Caggiano, 2005). In another analysis, the overall rate of death was 9.5%, with rates for solid tumor cancer patients ranging from 3.6% for breast cancer patients to 13.4% for lung cancer patients (Kuderer, 2006). Because both the severity and duration of neutropenia correlate with the risk of FN and infections (Bodey, 1966; Gustinetti, 2016; Li, 2016), a reduction in its occurrence and duration will decrease the risk of these events and provide an improved patient experience while receiving chemotherapy (Padilla, 2005).

6.2.3. Safety

Assessment of AEs, changes in laboratory parameters, electrocardiograms (ECGs), vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status are all standard assessments used in oncology trials to measure patient safety.

6.3. Rationale for Dose and Schedule of Study Treatment

Previous studies demonstrated the recommended Phase 2 dose of trilaciclib was 240 mg/m^2; the dose approved by the FDA for ES-SCLC. When trilaciclib was administered prior to chemotherapy to cancer patients, doses of 200 mg/m^2 (rounded up from 192 mg/m^2), 240 mg/m^2, and 280 mg/m^2 were evaluated. Trilaciclib exposures in cancer patients were slightly lower compared with healthy subjects, such that the dose of 240 mg/m^2 (rather than 200 mg/m^2) more closely matched the biologically effective dose of 192 mg/m^2. In addition, the dose of 240 mg/m^2 demonstrated maximal myeloprotection efficacy benefits (compared with 200 mg/m^2 and 280 mg/m^2) as measured by a variety of myelosuppression endpoints. The myeloprotective effect at 240 mg/m^2 was further evaluated and confirmed in three randomized controlled Phase 2 studies in SCLC patients. In addition, both the planned schedule and the planned doses of

trilaciclib were used in the previous TNBC study (G1T28-04) and demonstrated clinically meaningful benefits in OS duration. See the trilaciclib IB for details.

The 10 mg/kg dose and schedule of sacituzumab govitecan-hziy treatment is based on the instructions provided in the prescribing information (Trodelvy Package Insert, 2021).

Trilaciclib is always administered prior to systemic anti-cancer therapy on each day of anti-cancer therapy administration. Trilaciclib shall not be administered as monotherapy (i.e., on days that sacituzumab govitecan-hziy will be delayed or skipped).

6.4. Rationale for Patient Population

Metastatic TNBC is incurable. Historically, TNBC patients undergoing second-line therapy have had a very poor prognosis (PFS duration of 2 to 3 months and OS duration of 9 to 12 months). Chemotherapy is the mainstay of treatment of TNBC and there is no preferred or standard regimen used. While targeted therapies have greatly improved outcomes for hormone-positive and HER2-positive breast cancer, there remain patients with TNBC who do not benefit from these therapies. For example, although the PD-1/PD-L1 inhibitors in metastatic TNBC patients with PD-L1-positive tumors demonstrated superior efficacy leading to accelerated approval, this benefit does not extend to patients who have PD-L1 negative disease or who are PD-L1 positive, but for whom a PD-1/PD-L1 targeted treatment is not appropriate (Tecentriq® Package Insert, 2020). Additional available targeted therapies recently approved by the FDA are PARP inhibitors such as olaparib for the treatment of patients with germline BRCA-positive, HER2-negative metastatic breast cancer who have previously received chemotherapy (approved in January 2018) and talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer (approved in October 2018). While these two targeted therapies offer benefit to patients with TNBC, they are limited to those with germline BRCA mutations (~9-18% of TNBC patients; Hahnen, 2017). Treatment options are even more limited for patients who have received two or more regimens in the metastatic setting. Trilaciclib may provide a novel therapeutic option for these patients who have minimal options available. Offering TNBC patients an alternative therapeutic option that may provide a clinically meaningful extension of the duration of PFS or OS in the context of a manageable safety profile would be an important step forward for patients with locally advanced or metastatic TNBC who have received at least 2 prior treatments, at least 1 in the metastatic setting, regardless of PD-L1 status.

Trilaciclib enhances immune activation and promotes anti-tumor immunity by differentially arresting cytotoxic and regulatory T cell subsets followed by a faster recovery of cytotoxic T lymphocytes than regulatory T cells in tumors (Lai, 2020). This differential alteration of cell cycle kinetics between cytotoxic T lymphocytes and regulatory T cells results in a higher proportion of cytotoxic T lymphocytes than regulatory T cells, enhancement of T cell activation, and a decrease in regulatory T cell-mediated immunosuppressive functions (Chaikovsky and Sage, 2018; Deng, 2018; Goel, 2017; Schaer, 2018). Together, these events promote the cytotoxic T lymphocyte-mediated clearance of tumor cells. Therefore, the anti-tumor effects of trilaciclib might result from the transient proliferative arrest of T cells, followed by activation of cytotoxic T lymphocytes in the context of fewer regulatory T cells.

Based on the positive impact on OS duration observed in Study G1T28-04 (Table 3 and Table 4), in the context of trilaciclib's manageable safety profile, the addition of trilaciclib to sacituzumab

govitecan-hziy could provide a meaningful treatment option for patients with locally advanced or metastatic TNBC who have received at least 2 prior treatments, at least 1 in the metastatic setting and further evaluation of trilaciclib in this area of high unmet medical need is warranted.

6.5. Rationale for Sacituzumab Govitecan-hziy Therapy

As discussed in Section 4.1, while some breast cancer patients have targeted therapies available to them, sequential single-agent chemotherapy remains the standard of care for patients with metastatic TNBC (Cardoso, 2017; NCCN, 2020). Sacituzumab govitecan-hziy is an antibody-drug conjugate composed of a humanized anti–Trop-2 monoclonal antibody and a cleavable linker coupled to the cytotoxic chemotherapy SN-38, an active metabolite of the topoisomerase I inhibitor irinotecan and prevents re-ligation of topoisomerase I-induced single strand breaks (Starodub, 2015). The resulting DNA damage leads to apoptosis and cell death. Trop-2 (trophoblast cell-surface antigen) is a calcium signal transducer overexpressed in many epithelial cancers and implicated in the promotion of cellular proliferation, survival, and invasion (Barroso-Sousa, 2021). Trop-2 is expressed in breast cancer cells, including those in TNBC (Bardia, 2019), and high levels of Trop-2 expression are associated with poor prognosis and worse survival in breast cancer (Ambrogi, 2014). Sacituzumab govitecan-hziy contains on average 7 to 8 molecules of SN-38 per antibody molecule (Trodelvy Package Insert, 2021). Upon binding to Trop-2 expressing cancer cells, it is internalized and subsequentially releases SN-38 both intracellularly and in the tumor microenvironment (Bardia, 2019; Trodelvy Package Insert, 2021). This results in tumor cells recognized by sacituzumab govitecan-hziy being killed by intracellular uptake of SN-38, and adjacent tumor cells being killed by the extracellular release of SN-38 (Bardia, 2019).

In 2020, accelerated approval was granted by the FDA for sacituzumab govitecan-hziy for the treatment of adult patients with metastatic TNBC who have received at least two prior therapies for metastatic disease. The accelerated approval was based on results from the Phase 2 IMMU-132-01 trial where patients (N=108) treated with sacituzumab govitecan-hziy had an ORR of 33.3%, median DOR of 7.7 months (95% CI: 4.9-10.8 months), and 55.5% and 16.7% of patients having a DOR of ≥6 months and ≥12 months, respectively (Bardia, 2019). In 2021, full approval was granted by FDA based on the results from the Phase 3 ASCENT trial (Bardia, 2021). Median PFS for patients receiving sacituzumab govitecan-hziy was 4.8 months (95% CI: 4.1-5.8 months) compared with 1.7 months (95% CI: 1.5-2.5 months) in those receiving physician's choice of single-agent chemotherapy (HR 0.43, 95% CI: 0.35-0.54, P<0.0001) and median OS was 11.8 months (95% CI: 10.5-13.8 months) and 6.9 months (95% CI: 5.9-7.6 months), respectively (HR 0.51, 95% CI: 0.41-0.62, P<0.0001) (Trodelvy Package Insert, 2021). In that same study, in a subset of patients without brain metastasis at baseline (88% of the full study population), median PFS for patients receiving sacituzumab govitecan-hziy was 5.6 months (95% CI: 4.3-6.3 months) compared with 1.7 months (95% CI: 1.5-2.5 months) in those receiving physician's choice of single-agent chemotherapy (HR 0.41, 95% CI: 0.32-0.52, P<0.001) and median OS was 12.1 months (95% CI: 10.7-14.0 months) and 6.7 months (5.8-7.7 months), respectively (HR 0.48, 95% CI: 0.38-0.59, P<0.001) (Bardia, 2021).

Sacituzumab govitecan-hziy has provided an important new treatment option to patients with metastatic TNBC but is associated with some significant risks. Sacituzumab govitecan-hziy may cause severe diarrhea and severe or life-threatening neutropenia (Trodelvy Package Insert, 2021).

The addition of trilaciclib to sacituzumab govitecan-hziy may offer the potential for clinical benefit (increased survival) and an improved tolerability profile (myeloprotection) to patients with metastatic TNBC who have received at least 2 prior therapies, at least 1 in the metastatic setting.

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

In order to facilitate an unbiased evaluation of trilaciclib effects on the hematologic endpoints, primary prophylactic granulocyte colony-stimulating factor (G-CSF) will be prohibited in Cycle 1; however therapeutic G-CSF (administered in response to a neutropenic event) in Cycle 1 and secondary prophylactic G-CSF beginning in Cycle 2 and for all subsequent cycles (i.e., after a precipitating event in a prior cycle of therapy) will be allowed per growth factor/neutropenia management guidelines in Section 9.4.1 and Investigator discretion (Aapro, 2010; Smith, 2015).

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

The NCCN Human Growth Factor Supported Care Guidelines (NCCN, 2021) for patients receiving cytotoxic chemotherapy (including those in clinical trials) includes the following guidance for the use of trilaciclib as a supportive care intervention for patients with ES-SCLC. Trilaciclib as a supportive care intervention is being further investigated in this trial in patients with TNBC receiving sacituzumab govitecan-hziy treatment.

- Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (or G-CSF may be administered after) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for ES-SCLC.
- Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (*prophylactic* G-CSF may be administered after *Cycle 1*) platinum/etoposide ± immune checkpoint inhibitor-containing regimes or a topotecan-containing regimen for ES-SCLC.
- Trilaciclib may be used as a prophylactic option to decrease the incidence of *anemia and RBC transfusions* when administered before platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for ES-SCLC.

7. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

7.1. Inclusion Criteria

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

1. Age ≥18 years.
2. Female or male patient with measurable, unresectable locally advanced or metastatic TNBC.
3. Documentation of histologically or cytologically confirmed hormone (estrogen and progesterone) receptor negative tumor by immunohistochemistry (IHC) assessment (defined as <1% nuclei staining) and HER2-negative, non-overexpressing (by IHC [0 or 1+] OR in situ hybridization [ratio <2.0] OR average HER2 gene copy number of <4 signals/nucleus) per 2018 American Society of Clinical Oncology (ASCO) and the College of American Pathologists (ASCO/CAP) criteria. Patients with "estrogen receptor (ER) or progesterone receptor (PR) low positive" as per updated ASCO/CAP 2020 guidelines can be considered after approval by the Medical Monitor.
4. Measurable disease as defined by RECIST v1.1.
5. Considered to be eligible to receive sacituzumab govitecan-hziy treatment, in the Investigator's judgment.
6. Patients must have received 2 or more prior lines of systemic therapy, at least one of them in the metastatic setting.
7. Radiation therapy for metastatic disease is permitted as long as the patient has at least 1 measurable lesion that has not been irradiated. Patients should be sufficiently recovered from the effects of radiation as determined by the Investigator but must have completed radiotherapy at least 2 weeks prior to enrollment.
8. ECOG performance status of 0 or 1.
9. Adequate organ function as demonstrated by the following laboratory values:
    a. Hemoglobin ≥9.0 g/dL in the absence of RBC transfusion or ESA administration within 7 days prior to the first dose of trilaciclib;
    b. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
    c. Platelet count ≥100 × 10^9/L;
    d. Estimated glomerular filtration rate ≥30 mL/minute/1.73 m^2;
    e. Total bilirubin ≤1.5 × upper limit of normal (ULN);
    f. ALT and AST ≤3 × ULN in the absence of liver metastasis or ≤5 × ULN in the presence of liver metastasis.

10. Resolution of nonhematologic toxicities from prior systemic therapy, radiation therapy, or surgical procedures to Common Terminology Criteria for Adverse Events (CTCAE) ≤ Grade 1 (except alopecia or peripheral neuropathy that may be Grade 2 or less).
11. Predicted life expectancy of ≥3 months.
12. Contraceptive use by men or women should be consistent with local guidelines regarding the methods of contraception for those participating in clinical studies. Please see Section 17.3 for detailed instructions on methods of contraception requirements.
13. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

7.2. Exclusion Criteria

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

1. Prior treatment with trilaciclib, sacituzumab govitecan-hziy, irinotecan, Trop-2 antibody drug conjugate, or any therapy with a topoisomerase-1 payload.
2. Patients with known brain metastasis at enrollment.
3. Patients with known Gilbert's disease or known homozygous for the *UGT1A1*28* allele.
4. Patients with bone-only disease.
5. Malignancies other than TNBC within 3 years prior to enrollment. Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death <5% at 5 years as determined by the Investigator) are eligible provided they meet all of the following criteria:
    a. Malignancy treated with expected curative intent (e.g., adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent);
    b. No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers.
6. History of clinically significant gastrointestinal bleeding, intestinal obstruction, or gastrointestinal perforation within 6 months of enrollment.
7. Receipt of any investigational medication within 4 weeks, or at least 5 half-lives, whichever is greater, prior to the first dose of study treatment.
8. Receipt of any cytotoxic chemotherapy within 2 weeks or antibody treatment for cancer within 3 weeks prior to the first dose of study treatment.
9. Receipt of any high dose systemic corticosteroids within 2 weeks prior to the first dose of study treatment:
    a. Low dose corticosteroids (≤20 mg prednisone or equivalent daily) are permitted if the dose is stable for 4 weeks, or if medically indicated as part of their pre-medications for infusions.
    b. Topical steroids and corticosteroid inhalers are allowed.
10. Current use of immunosuppressive medication, EXCEPT for the following:

a. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);
b. Systemic corticosteroids at physiological doses ≤10 mg/day of prednisone or equivalent;
c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

11. Use of oral or IV antibiotics within 2 weeks prior to enrollment.
12. QT corrected interval using Fridericia's formula (QTcF) >480 msec at screening (confirmed on repeat). For patients with ventricular pacemakers, QTcF >500 msec.
13. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (Class III or IV as defined by the New York Heart Association functional classification system).
14. Known history of stroke or cerebrovascular accident within 6 months prior to first dose of study treatment.
15. Known serious active infection such as, but not limited to, human immunodeficiency virus (HIV) (e.g., viral load indicative of HIV, HIV 1/2 antibodies), Hepatitis B (e.g., Hepatitis B surface antigen reactive or Hepatitis B DNA detected), Hepatitis C (e.g., Hepatitis C ribonucleic acid [quantitative] is detected) or tuberculosis.
16. Severe infections within 4 weeks prior to enrollment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
17. 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.
18. Known hypersensitivity or allergy to irinotecan, SN-38, trilaciclib, or sacituzumab govitecan-hziy or any excipients of the aforementioned medications.
19. Prior hematopoietic stem cell or bone marrow transplantation.
20. Pregnant or lactating women:
    a. Women of childbearing potential must have negative serum pregnancy test result within 7 days prior to initiating study treatment.
21. Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to study treatment start, or anticipation of the need for major surgical procedure during the course of the study.
22. Received a live, attenuated vaccine within 4 weeks prior to the first dose of study treatment or anticipation that such a vaccine will be required during the study treatment period:
    a. Influenza vaccination should be given during influenza season only (approximately October through May in the Northern Hemisphere).
23. Legal incapacity or limited legal capacity.

24. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who are employees of G1 Therapeutics, Inc. directly involved in the conduct of the study.

8. PROTOCOL SCHEDULE OF ASSESSMENTS

The procedures and assessments to be performed during the study are outlined in Table 6. When there are multiple procedures at the same or overlapping time points, order of events should be: ECGs, vitals, blood draw.

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

Table 6: Schedule of Assessments

Assessment	Screening	Treatment Phase (1 cycle = 21 days)				Follow-Up Phase	See Protocol Section for Additional Details
		Every Cycle		End of Treatment Visit	Safety Follow-up	Survival Follow-Up	
	30 days prior to enrollment	Day 1	Day 8	14 days after last dose of study treatment (±7d)	30 days after last dose (+7d)	Every 3 months post-Safety Follow-up	
Informed Consent	X						Section 13.3
Enrollment		X [Cycle 1 (-7d)]					Section 11.1.2
Inclusion/Exclusion Criteria	X						Section 7
Demographics	X						Section 11.1.3
Medical History and Surgical History	X						Section 11.1.4
Concomitant Medications	X	X					Section 11.1.4
Complete Physical Examination (include weight and height)	X						Section 11.3.2
Symptom-directed Physical Examination (with weight only)		X					Section 11.3.2
Vital Signs	X	X		X			Section 11.3.1
ECOG Performance Status	X	X		X			Section 11.3.3
Adverse Event Reporting		X			X		Section 11.3.6
Laboratory Assessments and Procedures							
Hematology	X	X	X	X			Section 11.3.5
Chemistry	X	X [a]		X			Section 11.3.5
Pregnancy Test (WOCBP only)	X	X		X			Section 11.3.5
12-lead Electrocardiogram (in triplicate)	X	X [Cycle 1]	X [Cycle 1]				Section 11.3.4

Assessment	Screening	Treatment Phase (1 cycle = 21 days)				Follow-Up Phase	See Protocol Section for Additional Details
		Every Cycle		End of Treatment Visit	Safety Follow-up	Survival Follow-Up	
	30 days prior to enrollment	Day 1	Day 8	14 days after last dose of study treatment (±7d)	30 days after last dose (+7d)	Every 3 months post-Safety Follow-up	
Study Treatment							
Trilaciclib		X	X				Section 9.1
Sacituzumab govitecan-hziy		X	X				Section 9.1
Disease Assessment							
Tumor Assessments (CT/MRI)	X	X [b]					Section 11.2.1
Survival Follow Up and Subsequent Anti-Cancer Treatments						X	Section 11.7

CR=complete response; CT=computed tomography; d=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FDG=[^{18}F]-fluorodeoxyglucose; MRI=magnetic resonance imaging; NaF=sodium fluoride; PET=positron emission tomography; MRI=magnetic resonance imaging; Q6=every six; Q9=every 9; WOCBP=women of childbearing potential

[a] Chemistry samples will be collected every cycle during Cycles 1-4 and every other cycle (Cycle 6, Cycle 8, etc.) if results are stable, per Investigator discretion.

[b] CT/MRI of chest/abdomen/pelvis Q6 weeks (± 7d) through Week 36 relative to Cycle 1 Day 1 and Q9 weeks (± 7d) thereafter relative to Cycle 1 Day 1 until documented disease progression or subsequent anticancer therapy. Brain scan (MRI preferred) during screening is not required and should be performed per Investigator discretion based on clinical signs and symptoms. Additional brain MRI should be conducted if there are new clinical signs and symptoms suggestive of brain metastases. Bone metastases identified at baseline via a bone scan or PET (such as FDG-PET, NaF-PET, or other locally available PET options) to be followed at scheduled visits using localized CT or MRI as clinically indicated. If bone metastases cannot be seen on CT or MRI scans, bone scans or PET should be repeated, using the same diagnostic procedure bone metastases were at baseline, when CR is identified in target disease or when progression in bone is suspected.

9. STUDY TREATMENT

9.1. Study Drugs Administered

Study drugs are defined as any investigational product or chemotherapy intended to be administered to a study patient according to the study protocol. Study drugs used in this protocol are described in Table 7.

Table 7: Study Drugs

Name	Trilaciclib	Sacituzumab Govitecan-hziy
Type	Investigational Product	Chemotherapy
Dose Formulation	Single-use, sterile powder to be reconstituted and further diluted with 250 mL of normal saline (sodium chloride solution 0.9%) or dextrose 5% in water (D5W) per the Pharmacy Manual	See current prescribing information (Trodelvy Package Insert, 2021)
Unit Dose Strength(s)	300 mg/20 mL	See current prescribing information
Dosage Level(s)	240 mg/m^2 administered on Day 1 and Day 8 of each 21-day cycle	10 mg/kg reconstituted to a concentration of 1.1 mg/mL to 3.4 mg/mL in normal saline; total volume should not exceed 500 mL administered on Day 1 and Day 8 of each 21-day cycle. Protect from light.
Route of Administration	IV	IV
Infusion Time	30 minutes	3 hours for first infusion; 1 to 2 hours for subsequent infusions if prior infusions were tolerated

IV=intravenous

9.1.1. Dose, Dosing Regimen, and Route

Trilaciclib must be administered before sacituzumab govitecan-hziy.

9.1.1.1. Trilaciclib – Investigational Product

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

Trilaciclib must be reconstituted and further diluted prior to IV infusion as outlined in the Pharmacy Manual. Aseptic technique must be used for reconstitution and dilution. Upon reconstitution, the solution must then be diluted to the calculated dose based on the body surface area (BSA) of the patient. Actual body weight should be utilized for dose calculations. If there is a change in body weight ≥10% relative to the weight at the time of the last dose calculation, dose should be recalculated. Recalculation of dose more frequently per local institutional guidelines is permitted. Dose recalculation to adjust for changes in body weight will not be considered a dose reduction and will be made at the discretion of the

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

9.1.1.1.1. Administration of Trilaciclib

- Administer diluted trilaciclib solution as a 30-minute IV infusion no more than 4 hours prior to sacituzumab govitecan-hziy. Do not administer trilaciclib as a bolus.
- Trilaciclib is always administered first. Results from hematology labs should be reviewed prior to administration of trilaciclib. If administration of sacituzumab govitecan-hziy therapy is skipped or discontinued, trilaciclib will also be skipped or discontinued.
- Diluted trilaciclib solution must be administered with an infusion set, including an in-line filter (0.2 or 0.22 micron). Compatible in-line filters include polyether sulfone (PES), polyvinylidene fluoride, and cellulose acetate.
- Do not administer diluted trilaciclib solution with a polytetrafluorethylene (PTFE) in-line filter. PTFE in-line filters are not compatible with diluted trilaciclib solution.
- Do not co-administer other drugs through the same infusion line.
- Do not co-administer other drugs through a central access device unless the device supports co-administration of incompatible drugs.

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

The infusion rate may be decreased to manage an infusion-related AE; for example, if a patient experiences a burning sensation during infusion, the duration of infusion may be increased to 45 minutes (or longer if clinically indicated) to alleviate the symptoms. The actual start/stop time of infusion will be documented and entered in the eCRF.

9.1.1.2. Sacituzumab Govitecan-hziy – Chemotherapy

Descriptions of the formulations of commercially-available sacituzumab govitecan-hziy can be found in the respective current prescribing information. Protocol-specified doses of sacituzumab govitecan-hziy will be administered IV in accordance with institutional guidelines according to the study site's standard practice. Deviation from the recommendations provided in this protocol in order to follow institutional guidelines must receive prior approval from the Medical Monitor or Sponsor.

Actual body weight (not ideal body weight) should be utilized for dose calculations. At a minimum, if there is a change in body weight of >10% relative to the weight at the time of the last dose calculation, doses should be recalculated. Recalculation of the dose more frequently per local institutional guidelines is permitted. Dose recalculation to adjust for changes in body weight will not be considered a dose reduction.

Prior to each infusion of sacituzumab govitecan-hziy, premedication for the prevention of infusion reactions and CINV is recommended.

- Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.
- Premedicate with a two or three drug (preferred) combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated).

Administer the first infusion over 3 hours and observe patients during the infusion and for at least 30 minutes following the initial dose for signs or symptoms of infusion-related reactions. Subsequent infusions may be administered over 1 to 2 hours if prior infusions were tolerated, and patients should be observed during the infusion and for at least 30 minutes after infusion. Protect infusion bag from light. Do not administer as an IV push or bolus. The actual start/stop time of infusion will be documented and entered in the eCRF.

Trilaciclib is always administered first, followed by sacituzumab govitecan-hziy. Administer diluted trilaciclib solution as a 30-minute IV infusion to be completed within 4 hours prior to the start of sacituzumab govitecan-hziy. If administration of trilaciclib is delayed or discontinued, sacituzumab govitecan-hziy will also be delayed or discontinued. Likewise, if sacituzumab govitecan-hziy is delayed or discontinued, trilaciclib will also be delayed or discontinued.

9.1.2. Preparation, Handling, Storage, and Accountability

The Investigator or designee is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The Investigator/institution may assign some or all of the Investigator's/institution's duties for investigational product(s) accountability to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator/institution.

Further guidance and information are provided in the Pharmacy Manual.

9.1.3. Treatment Compliance

The Investigator or designee will dispense the study drugs, via a Pharmacist/Designee, only for use by patients enrolled in the study as described in this protocol. The study drugs are not to be used for reasons other than those described in this protocol. The clinical study site will maintain records of study drugs' receipt, preparation, and dispensing, including the applicable lot numbers; patient's height, body weight, and body surface area; date and time of the start of each trilaciclib and sacituzumab govitecan-hziy infusion; and total drug administered. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy (e.g., interruption of infusion without restarting) will be recorded on eCRF and in the source documents.

9.2. Criteria for Starting Cycle 1 and Each Subsequent Dose

Patients must meet all the following criteria to receive study treatment on Cycle 1 Day 1:

- ANC $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L

- Total bilirubin ≤1.5 × ULN
- AST/ALT ≤3 × ULN or ≤5 × ULN in the presence of liver metastasis
- Other nonhematologic drug-related toxicities must be ≤ Grade 1 (except alopecia or peripheral neuropathy that may be Grade 2 or less).

Patients must also have ANC ≥1.5 × 10^9/L to receive any Cycle Day 1 dose of study treatment and ANC ≥1.0 × 10^9/L to receive any Cycle Day 8 dose of study treatment.

9.3. Toxicity Management and Dose Modifications

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

The dose of sacituzumab govitecan-hziy can be reduced, when necessary, as described below. The recommended dose modification procedures for hematologic and non-hematologic toxicities are described in Table 8. If a subsequent cycle is delayed for toxicity, the patient should still complete the clinical laboratory assessments on the scheduled Day 1 (entered as an Unscheduled assessment in electronic data capture [EDC]) as well as on the actual first dosing day of that cycle. If the delay is secondary to hematologic toxicity, weekly repeat hematology assessments should continue until the finding meets criteria for resumption of dosing.

Treatment with sacituzumab govitecan-hziy will be permanently discontinued for a patient in the event of any Grade 4 infusion reactions which occur after pre-medication with antihistamines, H2 blockers, and steroids.

Recommendation for management of trilaciclib AESIs are provided in Table 9. Recommendations for hepatobiliary toxicity management are in Section 9.3.3.

For dose delays due to toxicity, the patient should be followed (at least) weekly, including CBCs if the AE is hematologic, to monitor the toxicity until treatment criteria are met or until they discontinue treatment. A 3-week delay from the scheduled dose of sacituzumab govitecan-hziy is permitted for toxicity and/or administrative reasons. As examples, if at the scheduled Cycle X Day 1 visit (e.g., Cycle 2 Day 1) a dose delay is needed for toxicity reasons, a delay up to 3 weeks from Cycle X Day 1 for sacituzumab govitecan-hziy is permitted; if at the scheduled Cycle X Day 8 visit (e.g., Cycle 1 Day 8) a dose delay is needed for toxicity reasons, a delay up to 3 weeks from Cycle X Day 1 for sacituzumab govitecan-hziy is permitted. Dosing delays >3 weeks from the scheduled dose of sacituzumab govitecan-hziy may be permitted on a case by-case basis with the documented approval of the Investigator and Medical Monitor.

All recommendations are intended as a minimum guideline for toxicity management and are not a replacement for independent medical judgment tailored to specific circumstances with an individual patient. Please also refer to the individual package insert (Trodelvy Package Insert, 2021) for additional information and recommendations.

Study drug administration will continue until progressive disease per RECIST v1.1 or clinical progression as determined by the Investigator, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the study, whichever occurs first.

9.3.1. Recommended Actions with Sacituzumab Govitecan-hziy for Adverse Events

Recommended dose levels for reduction of sacituzumab govitecan-hziy dose are described below. Sacituzumab govitecan-hziy dose reductions for hematologic toxicities are based on values obtained within 24 hours prior to Day 1 or Day 8 of a given cycle per Investigator discretion and institutional guidelines; recommendations are provided in Table 8. All dose reductions for an individual patient are permanent; and the dose, which has been reduced for toxicity, must not be re-escalated. Up to a maximum of 2 dose reductions will be allowed per patient. If a third dose reduction is required per the modifications below, the patient should discontinue study treatment.

- Starting dose: 10 mg/kg
- First dose reduction: 25% from original dose
- Second dose reduction: 50% from original dose
- Third dose reduction: discontinue all study drugs

Note that dose modifications (specifically dose reductions/discontinuations) are recommended for those events considered related to drug (i.e., toxicities) such that decreasing the dose or stopping the drug will lead to improved patient safety. If an event is not thought to be related to study drug by the Investigator, dose reduction/discontinuation is not required since decreasing the dose or stopping the drug would not be expected to alter the risk of the event occurring again; rather, the Investigator should consider if treatment should be delayed until the event recovers to ≤Grade 1 or baseline before resumption of treatment. Decreased neutrophil, platelet counts or hemoglobin values that occur in isolation (e.g., at nadir) that do not result in a dosing delay, febrile neutropenia, serious adverse event (SAE) or other consequence, do not require dose modification.

If drug-related toxicity requires discontinuation of sacituzumab govitecan-hziy or trilaciclib then the patient must permanently discontinue all study drugs and should complete the Post-Treatment Visit and enter Survival Follow-up.

Table 8: Recommended Dose Modifications for Sacituzumab Govitecan-hziy

Adverse Event	Occurrence	Dose Modification
Severe Neutropenia		
Grade 4 neutropenia ≥7 days OR Grade 3 febrile neutropenia (ANC <1000/mm^3 and fever ≥38.5°C) OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤Grade 1	First	25% dose reduction and administer G-CSF
	Second	50% dose reduction
	Third	Discontinue treatment
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤Grade 1	First	Discontinue treatment
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration OR Any Grade 3-4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents OR Grade 3-4 non-hematologic toxicity persisting >48 hours despite optimal medical management OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤Grade 1 within 3 weeks	First	Discontinue treatment

ANC=absolute neutrophil count; G-CSF=granulocyte colony-stimulating factor
Source: Table recreated from Trodelvy Package Insert, 2021

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

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

Table 9: Recommended Actions with Trilaciclib Following AESIs

AESI	Severity	Recommended Action
Injection site reactions including phlebitis and thrombophlebitis	Grade 1: Tenderness with or without symptoms (e.g. warmth, erythema, itching)	Interrupt or slow infusion of trilaciclib. If 0.9% normal saline is being used as a diluent/flush, consider changing to 5% dextrose as appropriate for subsequent infusions.
	Grade 2: Pain; lipodystrophy; edema; phlebitis	Interrupt infusion of trilaciclib. If pain not severe, follow instructions for Grade 1. Otherwise, stop infusion in extremity and rotate site of infusion to site in alternative extremity. If 0.9% normal saline is being used as a diluent/flush, consider changing to 5% dextrose as appropriate for subsequent infusions. Central access may also be considered.
	Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated. Grade 4: Life threatening consequences; urgent interventions indicated.	Stop infusion and permanently discontinue trilaciclib.
Acute drug hypersensitivity reactions	Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting ADL	Stop infusion and hold trilaciclib until recovery to Grade ≤1 or baseline, then consider resuming trilaciclib. If Grade 2 recurs, permanently discontinue trilaciclib.
	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL OR Grade 4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue trilaciclib.
ILD/pneumonitis	Grade 2 (symptomatic)	Hold trilaciclib until recovery to Grade ≤1 or baseline, then consider resuming trilaciclib. If Grade 2 recurs, permanently discontinue trilaciclib.

AESI	Severity	Recommended Action
	Grades 3: Severe symptoms; limiting self-care ADL; oxygen indicated OR Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue trilaciclib.

AESI=adverse event of special interest; ADL=activities of daily living; ILD=interstitial lung disease

9.3.3. Hy's Law Management

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

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to determine the etiology of the abnormal laboratory values:

- Baseline AST or ALT and total bilirubin values are within the normal range and the patient subsequently presents with AST or ALT ≥3 × ULN concurrent with a total bilirubin ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 × ULN or not available.
- Preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, and the patient subsequently presents with:
  - AST or ALT ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller)
  - Concurrent with total bilirubin increased by one time the baseline value OR ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted.

All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be promptly reported as SAEs via the EDC.

9.4. Supportive Care Interventions

9.4.1. Colony Stimulating Factor Usage

Use of prophylactic colony stimulating factors (e.g., G-CSF; granulocyte-macrophage colony-stimulating factor [GM-CSF]) during Cycle 1 (i.e., prior to the actual Cycle 2 Day 1 dosing visit) is not allowed. In subsequent cycles (Cycle 2 and beyond), prophylactic colony-stimulating factors are allowed as outlined in Table 8, which are based on the ASCO guidelines for neutropenia (Smith, 2015) and package inserts. If in any cycle (including Cycle 1), a patient experiences severe neutropenia (Grade 4) or febrile neutropenia and is at high risk for infection-associated complications, or has prognostic factors that are predictive of poor clinical outcomes (Table 10), G-CSF/GM-CSF may be used to treat the severe neutropenia or febrile neutropenia event per ASCO guidelines and package inserts.

Short-acting G-CSF products (i.e., Neupogen or biosimilars) may be administered starting 24 to 48 hours after sacituzumab govitecan-hziy and must be stopped 48 hours prior to study drug administration in the next cycle. Similarly, Neulasta (or biosimilars) or other long half-life G-CSF products (e.g., macapegfilgrastim) may be administered 24 to 48 hours after sacituzumab govitecan-hziy but due to its prolonged half-life should not be repeated within that cycle.

Table 10: 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 $<0.1 \times 10^9$/L)
Neutropenia expected to last >10 days
Pneumonia
Invasive fungal infection
Other clinically documented infections
Hospitalization at time of fever
Prior episode of febrile neutropenia

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

9.4.2. Erythropoiesis-Stimulating Agent Usage

If a patient experiences chemotherapy-induced anemia (hemoglobin level <10 g/dL) after receiving the first dose of study treatment, ESAs may be used per ASCO guidelines and the current prescribing information (Bohlius, 2019) (Procrit®, 2017; Aranesp®, 2011).

9.4.3. Transfusions

Red Blood Cells

Based on the NCCN Clinical Practice Guidelines in Oncology for Hematopoietic Growth Factors Version 2.2020 and the AABB Clinical Practice Guidelines, the following RBC transfusion thresholds are recommended (Carson, 2016; Goel, 2018); however, the patient's clinical situation should always be the primary guiding factor when deciding to transfuse.

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

Platelets

Platelet transfusion is recommended at a threshold of ≤10 x 10^9/L. Platelets should also be transfused in any patient who is bleeding with a platelet count <50 x 10^9/L (100 x 10^9/L for central nervous system or ocular bleeding) (Kaufman, 2015; Schiffer, 2001).

9.5. Prior/Concomitant Medications and Procedures

All prior and concomitant medications including prescription medications, over-the-counter preparations, supplements, herbal remedies, growth factors, and blood products from informed consent through 30 days after the last dose of study treatment (Safety Follow-up Visit) will be documented, where possible.

Avoid concomitant use of trilaciclib with certain OCT2, MATE1, and MATE-2K substrates (e.g., dofetilide, dalfampridine) where minimal concentration changes may lead to serious or life-threatening toxicities. Refer to the prescribing information for these concomitant medications for assessing the benefit and risk of concomitant use of trilaciclib.

Avoid administering UGT1A1 inhibitors with sacituzumab govitecan-hziy. Concomitant administration of sacituzumab govitecan-hziy with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38.

Avoid administering UGT1A1 inducers with sacituzumab govitecan-hziy. Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers.

Administration of other concomitant investigational agents for any indication or any live attenuated vaccines is not permitted while on this study. Necessary supportive care (antiemetics, antidiarrheals, chemotherapy premedication, etc.) per the standard of care at the study center will be permitted. See Section 9.4 for guidance on the use of growth factors (colony-stimulating factors and ESAs) during the study.

Administration of other systemic concomitant non-protocol anticancer therapies prior to progression is not permitted while on this study. Palliative treatment of a symptomatic

lesion(s) is permitted to control disease symptoms but not to aid in the response of the tumor. If the lesion(s) treated is being followed for evaluation by RECIST v1.1 (target or nontarget lesion), then "not evaluable" should be reported in EDC for this lesion at subsequent disease assessments following palliative treatment. Patients requiring palliative therapy may continue receiving study drug until documented disease progression (radiographic or clinical) if, in the Investigator's opinion, the patient is continuing to receive clinical benefit and they meet the requirements described in Section 9.2. However, for patients who have not had disease progression at the time of the need for palliative radiation therapy or surgery, the requirement for intervention will be regarded as disease progression in the study's analyses and will be entered as such in the EDC.

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

9.6. Measures to Minimize Bias

The study will be single-arm and open-label.

Patients that are enrolled, received at least one dose of study drug, and discontinue from the study will not be replaced. Patients that are enrolled but did not receive any study drug may be replaced upon approval of the Medical Monitor and Sponsor.

9.7. Intervention after End of Study Treatment

Following completion of study treatment on the study, patients will receive treatment as determined by their healthcare provider. During Survival Follow-up, the patient (or legally authorized representative where allowed by local regulation) will be contacted to record their status (alive or dead) as well as details of any subsequent systemic anti-cancer therapy initiated (see Section 11.7).

10. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

10.1. Discontinuation of Study Treatment

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

- A patient suffers an AE that, in the judgment of the Investigator, Sponsor, or Medical Monitor, presents an unacceptable risk to the patient
- General or specific changes in the patient's condition (e.g., a significant intercurrent illness or complication) that, in the judgment of the Investigator, are unacceptable for further administration of study drug
- Occurrence of pregnancy in a female patient during the study
- Significant noncompliance with protocol requirements
- The Sponsor or legal representative of the Sponsor requests the patient to withdraw
- Patient has documented disease progression (radiographic or clinical progression). See Section 9.5 for details regarding palliative therapy.
- If the total time from a scheduled sacituzumab govitecan-hziy dose exceeds a total of >3 weeks, unless agreed to by the treating Investigator and Medical Monitor.
- Where permanent discontinuation of any study drug is indicated in the toxicity management recommendations (Section 9.3).

At the time of study drug discontinuation, an End of Treatment Visit should be completed with assessments performed as shown in the Schedule of Assessments (Table 6). The Investigator or Designee will document the reason for study drug discontinuation on the applicable eCRF. When discontinuation is due to a SAE or a Grade 3 or 4 toxicity considered to be related to study drug, the Investigator should follow the event until resolution, return to baseline, or it is deemed that further recovery is unlikely. Data on these events should be collected on the AE eCRF. In the event a patient discontinues due to pregnancy, the Investigator or designee should notify the Medical Monitor by telephone within 24 hours of pregnancy confirmation (see Section 17.3).

For those patients who have not progressed clinically or radiologically at the time of study drug discontinuation, every effort should be made to continue radiological tumor assessments every 12 weeks (±7 days) during survival follow-up, utilizing the same imaging modality as used at Screening as outlined in the Schedule of Assessments (Table 6), until progressive disease, initiation of subsequent anti-cancer therapy, withdrawal of consent, or study completion, whichever occurs first. Results of these scans should be assessed by RECIST v1.1 and data entered in EDC in the corresponding tumor assessment forms.

10.2. Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance,

or administrative reasons. At the time of discontinuing from the study, if the patient has not already discontinued study intervention, an End of Treatment Visit should be completed with assessments performed as shown in the Schedule of Assessments (Table 6).

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

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

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

10.3. Lost to Follow Up

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

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

10.4. Study and Site Start and Closure

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

A study site is considered eligible to start participation in the study once all regulatory approvals are in place, site agreement contract is fully executed, and any other required documents are in place as required by Sponsor.

The end of study is event driven. That is, unless otherwise decided by the Sponsor, the study will continue until approximately 70% of patients enrolled in the study have died, which is estimated to be approximately 30 months after the first patient is enrolled.

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

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

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

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

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

11. STUDY ASSESSMENTS

Study procedures and their timing are summarized in the Schedule of Assessments (Table 6). Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Immediate safety concerns should be discussed with the study Medical Monitor upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

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

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

11.1. Screening Assessments

The following information for screening failures should be recorded into appropriate eCRFs: patient identification (ID), demographic data, inclusion/exclusion criteria, eligibility status, and SAEs (if any). Patients may only be rescreened one time at the discretion of the Investigator. For abnormal laboratory values, a second test to confirm the first is permitted.

11.1.1. ER-, Progesterone Receptor-, HER2-Negative Status

Eligibility will be based on local ER-negative, progesterone receptor-negative, HER2-negative status from the most recent tumor biopsy report obtained prior to Screening.

Estrogen receptor/progesterone receptor negative status should be histologically or cytologically confirmed by local pathology IHC assessment (defined as <1% nuclei staining) and HER2 non-overexpressing status should be confirmed by local assessment of IHC (0 or 1+), by *in situ* hybridization (ratio <2.0), or by average HER2 gene copy number of <4 signals/nucleus) per 2018 ASCO CAP criteria.

11.1.2. Enrollment

Eligibility will be determined prior to enrollment and the start of study treatment. All eligible patients will receive a unique patient ID number. Once a patient ID is assigned to patient, it can never be reassigned to another patient.

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

Enrollment will be performed via Interactive Web Response System following confirmation that the patient is eligible for the study.

11.1.3. Demographics

Age, gender, race, and ethnicity will be collected during the Screening period.

11.1.4. Medical History and Breast Cancer Disease History

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

Documentation of TNBC history, including date of diagnosis as well as BRCA classification (if available), will be collected.

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

11.2. Efficacy Assessments

11.2.1. Anti-tumor Efficacy Assessment

All sites of measurable and non-measurable disease must be documented at Screening and re-assessed at each subsequent tumor evaluation. Tumor assessment will be performed at the timepoints relative to Cycle 1 Day 1, as specified in the Schedule of Assessments (Table 6), regardless of drug (cycle) delays, skips, or interruptions. Tumor assessments will continue until disease progression, withdrawal of consent, initiation of subsequent anti-cancer therapy, or study completion, whichever occurs first.

Baseline imaging must include CT or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. CT scans with IV contrast are the preferred method unless contraindicated (i.e., patients with contrast allergy or impaired renal clearance) and oral contrast may be used per Investigator's discretion. MRIs of the chest, abdomen, and pelvis with a noncontrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated. Bone scan or positron emission tomography (PET) scan (such as [^{18}F]-fluorodeoxyglucose [FDG]-PET, sodium fluoride [NaF]-PET, or other locally available PET options) must also be performed in all patients to evaluate for bone metastases at baseline. At the Investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used. Any CT, MRI, or bone imaging (bone scan or PET scan) obtained as standard of care prior to Screening visit will not need to be repeated as long as those imaging tests were obtained within 30 days prior to the date of enrollment.

After baseline tumor assessments, evaluation of tumor response per RECIST v1.1 will be performed every 6 weeks for the first 36 weeks following Cycle 1 Day 1 (±7 days) and every 9 weeks thereafter (±7 days), with additional scans performed as clinically indicated.

Post-baseline tumor assessments should use the same imaging modality (CT or MRI) as at baseline. Patients with bone metastases identified on the baseline bone scan or PET scan should be followed at scheduled visits using localized CT or MRI as clinically indicated. If the patient has bone metastases on the baseline bone scan or PET scan but are not visualized on CT or MRI, the same bone imaging modality (bone scan or PET scan) should be repeated when a complete response is identified in target disease or when progression in bone is suspected (Table 6).

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

For those patients who have not progressed clinically or radiologically at the time of study drug discontinuation, every effort should be made to continue radiological tumor assessments, utilizing the same imaging modality as used at Screening.

11.2.2. Myeloprotection Assessments

The myeloprotective effects of trilaciclib when administered prior to sacituzumab govitecan-hziy will be evaluated based on the following: occurrence of SN; hematologic toxicities, including febrile neutropenia; RBC and platelet transfusions; hematopoietic growth factor utilization; infections and systemic antibiotic use; dose reductions/delays. All of these variables will be assessed as described in the safety assessments (monitoring of AEs, clinical laboratory assessments, and concomitant medications).

11.3. Safety Assessments

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

11.3.1. Vital Signs

The following will be collected per the Schedule of Assessments (Table 6) within 10 minutes prior to the start of sacituzumab govitecan-hziy infusion, 30 minutes after the start of the sacituzumab govitecan-hziy infusion (±5 minutes), and at the end of the sacituzumab govitecan-hziy infusion:

- Body temperature, pulse rate, blood pressure (diastolic and systolic)

Height in centimeters (Screening visit only) and body weight in kilograms will also be collected.

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

11.3.2. Physical Examination

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

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

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

11.3.3. ECOG Performance Status

The Investigator or qualified designee will assess ECOG performance status during the Screening Period to assess for eligibility according to the inclusion and exclusion criteria (Table 11) as well as to monitor performance throughout the study (Table 6).

Table 11: ECOG Performance Status

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

ECOG=Eastern Cooperative Oncology Group
Source: Oken, 1982.

11.3.4. Electrocardiogram

Standard 12-lead ECGs will be performed in triplicate at Screening and on Day 1 and Day 8 of Cycle 1 at the following timepoints: pre-dose (any time prior to trilaciclib on the day of dosing), at the end of trilaciclib infusion (but prior to initiation of sacituzumab govitecan-hziy infusion), and at the end of sacituzumab govitecan-hziy infusion (Table 6). Additional ECGs may be performed as clinically indicated at any time during the study. All 12-lead ECGs will be obtained after the patient has been resting for at least 10 minutes and shall be recorded at 25 mm/sec. All ECGs for an individual patient shall be recorded with the patient in the same physical position.

Any ECG with a QTc value of >500 msec shall have the QTc value confirmed via manual read. The Investigator or qualified designee should review the ECGs for any abnormalities as compared with the baseline ECG. Following confirmation, the Investigator should evaluate for any other potential causes of the prolongation (e.g., concomitant medications) and determine the appropriate clinical course.

The Investigator or qualified designee shall review the ECGs for any abnormalities as compared with the baseline ECG.

11.3.5. Clinical Safety Laboratory Assessments

Hematology, chemistry, and pregnancy tests will be performed at the site's local certified laboratory per the schedule outlined in the Schedule of Assessments (Table 6). Clinical laboratory samples may be collected from patients at a different location than Investigator's clinic following approval by the Medical Monitor. A list of clinical laboratory tests to be performed is provided in Section 17.1.

Hematology may be obtained up to 24 hours and chemistry may be obtained up to 72 hours prior to each time point on Schedule of Assessments. For women of childbearing potential, pregnancy tests will be performed as follows: serum beta human chorionic gonadotropin (ß-hCG) at Screening and serum or urine ß-hCG on Day 1 of each treatment cycle, and at the End of 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.

Chemistry and hematology results shall be reviewed before dosing. Laboratory toxicities will be assessed using the National Cancer Institute (NCI)-CTCAE v5.0.

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

If a subsequent cycle is delayed/skipped for toxicity, the patient should still complete the clinical laboratory assessments on the scheduled Day 1 (entered as an Unscheduled assessment in the eCRF) as well as on the actual first dosing day of that cycle. If the delay is secondary to hematologic toxicity, weekly repeat hematology assessments should continue until the finding meets criteria for resumption of dosing (see Section 9.2; Table 8).

11.3.6. Adverse and Serious Adverse Events

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up, as applicable, AEs that are serious, considered related to the study drugs or study procedures, or that caused the patient to discontinue the study or study drugs (see Section 10.1). Patients should be encouraged to report AEs freely or in response to general, nondirected questioning. Adverse events (serious and non-serious) should be reported on the appropriate page of the eCRF. Toxicity will be assessed by Investigators using NCI-CTCAE v5.0.

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

AEs will be collected starting from the first dose of study drug through the Safety Follow-up Visit. Any SAE occurring between the date the patient signs informed consent and the first dose of any study drug, and which the Investigator feels is related to a study specific procedure (i.e., would not have occurred unless the patient was on the study), should also be reported. Any AEs that occur between the date of signing informed consent and the first dose of study drug should be recorded as Medical History.

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

Investigators are not obligated to actively seek AE or SAE information after 30 days following the last dose of study drugs on this study. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator or designee must promptly notify G1 Therapeutics PVG or designee.

11.3.6.2. Method of Detecting Adverse and Serious Adverse Events

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

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

11.3.6.3. Follow-up of Adverse and Serious Adverse Events

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

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

11.3.6.4. Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

11.3.6.5. Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study intervention and until 30 and 120 days respectively, after the last dose of study drug.

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

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

11.4. Safety Monitoring Committee

An independent SMC will monitor accumulating safety and disposition data with the first meeting planned for when approximately 10 patients have completed at least 2 cycles of study treatment. The meetings will continue when approximately 25 enrolled patients have completed at least 2 cycles of study treatment and again when all enrolled patients have completed at least 2 cycles of study treatment or as defined in the SMC charter. Additional reviews may occur.

A single SMC charter will define the roles and responsibilities of the SMC and its members. Additional details regarding the committee's composition, scope, objectives, procedures, and policies, including data to be reviewed are described in the SMC charter. The SMC will monitor accumulating safety and disposition data and will be comprised of study team members and independent members.

11.5. End of Treatment Visit

When a patient permanently discontinues study treatment, the patient should complete an End of Treatment Visit 14 days (±7 days) from last dose of study drug as outlined in Table 6.

11.6. Safety Follow-up Visit

The patient should complete a Safety Follow-up Visit 30 days (+7 days) from last dose of study drug as outlined in Table 6. This visit may occur at the study site, or can be via telephone, email, or by receiving information from a family member or healthcare provider.

11.7. Survival Follow-up Phase

After completion of the Safety Follow-up Visit, the patient will be followed approximately every 3 months for survival. Survival Follow-up Visits can be via telephone, email, or clinic visits.

Information will be collected until the end of the study (or death) to record the patient's status (alive or dead). In addition, details of any subsequent systemic anti-cancer therapy initiated, including name(s) of agent(s), dates (start/stop) administered, best response to the treatment, and date of progression should also be reported to the best of their ability.

If a patient withdraws consent for further study procedures, the site should clarify if the patient (or legally authorized representative where allowed by local regulation) remains open to survival contact and associated data collection. Provided that the patient has not withdrawn consent for follow up contact, information from medical records may be substituted for phone or other contact, provided that records are available as source documentation. Public records may be used to verify survival status if permitted by institutional or country guidances.

12. STATISTICAL CONSIDERATIONS

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

12.1. Sample Size Determination

The sample size is calculated to support the primary objective of the study, that is, to evaluate trilaciclib's effect on PFS when administered prior to sacituzumab govitecan-hziy in patients with locally advanced or metastatic TNBC who received at least 2 prior treatments with at least 1 in the metastatic setting.

This single-arm study plans to enroll 45 patients during the 10-month accrual period with an approximate 30-month total study duration. With 45 patients and 14 months of follow-up after the last patient is dosed, Table 12 presents the required number of PFS events and statistical powers to detect HRs of 0.7 and 0. 8 at a 2-sided significance of 0.2 for a median PFS of the historical control group of 5.6 months, which was defined for patients without brain metastases treated with sacituzumab govitecan-hziy in the Phase 3 ASCENT trial (Bardia, 2021). The calculation is based on one-sample log-rank test (Wu, 2015) with the assumption that the survival time distributions for both study treatment and historic control group follow the Weibull distribution with a shape parameter of 1.00 (i.e., exponential distribution).

Table 12: Statistical Power

Hazard Ratio	Median PFS for trilaciclib + sacituzumab govitecan-hziy (Months)	Expected number of events in the study	Statistical Power
0.70	8.0	36	80%
0.80	7.0	38	54%

12.2. Analysis Population

The following analysis populations are defined for the study.

The full analysis set (FAS) includes all enrolled patients who were administered at least 1 dose of study drug. Unless otherwise specified, the FAS is the primary analysis set for all efficacy analyses.

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

The safety population includes all enrolled patients who received at least 1 dose of study drug. All safety analyses will be evaluated using the safety population.

12.3. Timing of Planned Analysis

12.3.1. First Planned Analysis – Analyses for Progression-Free Survival, Tumor Response Endpoints, and Myelosuppression Endpoints

The first planned analysis will be conducted for the primary endpoint, PFS, at the time when 36 patients have radiographically-determined disease progression or have died. Study database will be locked to support the analysis. In addition, the following specified analyses will be performed:

- Analysis of tumor response endpoints (ORR, CBR, and DOR).
- Analysis of myelosuppression endpoints.
- Analysis of safety data.

12.3.2. Final Planned Analysis – Analysis for Overall Survival

Analysis for OS will be conducted when approximately 70% of patients have died (i.e., 32 deaths). Study database will be locked to support the final OS analysis.

12.4. Statistical Analysis Methods

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

12.4.1. General Considerations

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

12.4.2. Patient Disposition

Patient disposition will be summarized. The summary will include number of all screened patients, and number and percentage of patients who were enrolled, received study drug, discontinued from each study drug and the reasons, and discontinued from the study and reasons.

12.4.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS. The summary will include age, age groups, gender, race, ethnicity, screening vital signs (body weight, height, body mass index, BSA), ECOG status (0-1), number of previous chemotherapy regimens or advanced disease.

12.4.4. Prior and Subsequent Anticancer Therapies

Prior and subsequent anticancer therapy verbatim terms will be coded to Anatomical Therapeutic Classification and preferred term using the latest version of World Health

Organization-Drug Dictionary. For the FAS, summary statistics will be provided for prior and subsequent systemic anti-cancer therapies. For the subsequent systemic anti-cancer therapies, the lines of therapy, best response to each treatment regimen, and disease progression status will also be summarized.

12.4.5. Study Drug Exposure, Modification and Dose Intensity

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

Duration of study drug exposure will be defined for sacituzumab govitecan-hziy and for trilaciclib and summarized. The number of cycles that patients have received will be summarized by descriptive statistics as a continuous variable, while the number of cycles that are completed will be summarized as a categorical variable.

Study drug modifications will be summarized in three categories: sacituzumab govitecan-hziy dose reductions, sacituzumab govitecan-hziy cycle delay, and infusion interruption. The number and percentage of patients who have any sacituzumab govitecan-hziy dose reductions will be summarized; the number and percentage of patients who have at least one cycle delay will be summarized along with a summary of the number of cycles that have been delayed; the number and percentage of patients who have at least one infusion interruption for trilaciclib or sacituzumab govitecan-hziy will be summarized along with a summary of the number of interruptions. Lastly, the primary reason for each form of study drug modification (sacituzumab govitecan-hziy dose reductions, cycle delay, and infusion interruption) will also be summarized.

For trilaciclib and sacituzumab govitecan-hziy, cumulative dose, dose intensity, relative dose, and relative dose intensity will be derived and summarized.

12.4.6. Efficacy Analyses

12.4.6.1. Analyses of Primary Efficacy Endpoint – Progression-Free Survival

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

The primary analysis for PFS will be conducted at the time when 36 patients have radiographically-determined disease progression or have died. A Kaplan-Meier plot will be produced. The median, 25%, and 75% percentile of PFS will be estimated using the Kaplan-Meier method with their corresponding 95% CI calculated using the method by Brookmeyer and Crowley (1982).

Analysis of PFS during the study will be based on the FAS.

12.4.6.2. Analyses for Secondary Anti-tumor Efficacy Endpoints

Secondary anti-tumor endpoints include the following:

- Tumor response related endpoints
  - Objective response rate (ORR)
  - Clinical benefit rate (CBR)
  - Duration of objective response (DOR)
- Overall survival (OS)

Analysis for Tumor Responses

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

The number and percentage of patients in each category of derived BOR (confirmed complete response (CR), confirmed partial response (PR), stable disease (SD), PD, or Not Evaluable) will be summarized.

ORR is defined as the proportion of patients with BOR of confirmed CR or confirmed PR. ORR, along with its exact 95% two-sided CI using the Clopper-Pearson method, will be computed. ORR will be analyzed based on the RE population.

CBR is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR or SD lasting 24 weeks or longer from the first date of study drug administration. The analysis of CBR will be performed using the methods similarly to ORR.

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

Analysis for OS

Overall survival is defined as the time (months) from the date of first dose of study drug to the date of death for patients who died in the study due to any cause or the time to the last contact date known to be alive for those patients who survived as of the data cutoff date for the planned OS analysis (censored cases). For patients who drop out of the study right after enrollment, their survival time is censored at the date of enrollment. OS will be conducted at the time when approximately 70% of patients (~32 patients) have died. Survival distribution

of OS will be based on Kaplan-Meier method used for the analysis for PFS. In addition, the number and percentage of patients who died or censored will be summarized along with the eCRF collected reasons for death. The total duration of follow-up will also be summarized.

The analysis for OS will be based on the FAS.

The analysis for ORR, DCR and DOR will be based on the RE population.

12.4.6.3. Analysis of Myelosuppression Endpoints

Myelosuppression endpoints are grouped by lineage and consequence as follows:

- Neutrophils related (including occurrence of SN [during Cycles 1/2 and the overall study], occurrence of FN, and occurrence of G-CSF administration)
- RBC related (including occurrence of Grade 3/4 decrease of hemoglobin, occurrence and number of RBC transfusions on/after Week 5, and occurrence of ESA administration)
- Platelet related (including occurrence of Grade 3/4 decrease of platelets, occurrence and number of platelet transfusions)
- Endpoints related to trilaciclib's effect on dosing or hospitalizations due to chemotherapy-induced myelosuppression (including occurrence and number of dose reductions, or dose delay)

The analysis of myelosuppression endpoints will be based on the FAS.

Binary Myelosuppression Endpoints:

For the binary myelosuppression endpoints (e.g., the occurrence of SN and the occurrence of RBC transfusions on/after Week 5), the number and percentage of patients with at least one occurrence during the treatment period will be summarized by treatment group.

Counting Myelosuppression Endpoints:

For counting myelosuppression endpoints (e.g., the number of RBC transfusions on/after Week 5, and the number of dose reductions during the treatment period), the total number of the event, the total duration of treatment period (either in the unit of weeks or cycles), and event rate per 100 weeks or cycles will be summarized. For example, the event rate for RBC transfusions on/after Week 5 will be reported per 100 weeks and that for dose reduction will be reported per100 cycles. For a given event, patients without any events during the treatment period will be assigned a value 0 to be included in the analysis.

12.4.7. Safety Analyses

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

12.4.7.1. Adverse Events

AEs are defined as those events occurring or worsening after treatment has begun on this study. Adverse event data will be coded to system organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The severity (toxicity grades 1-5) of AEs will be graded by Investigators according to the NCI-CTCAE Version 5.0. The number and percentage of patients experiencing any AE, AEs related to study drug (trilaciclib or sacituzumab govitecan-hziy) as assessed by the investigator, AEs leading to study drug discontinuation, dose modification, and trilaciclib AESIs will be summarized by system organ class, preferred term, and NCI-CTCAE grade, when appropriate. In the tabulation of toxicity grade and causality, if the same AE occurred on multiple occasions for a patient, the highest grade and strongest relationship to study drug will be used in a summary. Trilaciclib AESI categories have been recognized, reflecting either the findings in the AEs from the previous studies of trilaciclib or class effects for CDK4/6 inhibitors. AESI for trilaciclib that will be reported from this study will be identified by searching MedDRA preferred terms based on the Customized MedDRA Queries that will be detailed in the study SAP.

12.4.7.2. Other Safety Endpoints

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

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

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

13. ETHICS

13.1. Ethics Review

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

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

The Investigator will be responsible for the following:

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

13.2. Ethical Conduct of the Study

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

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

13.3. Written Informed Consent

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data Protection

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

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

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

14.2. Data Quality Assurance

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

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

14.3. Dissemination of Clinical Study Data

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

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

14.4. Source Documents

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

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

14.5. Audits and Inspections

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

15. PUBLICATION POLICY

By signing the study protocol, the Investigator and his or her institution agree that the results of the study may be used by G1 Therapeutics 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. G1 Therapeutics reserves the right to request modification of any publication, presentation or use by the Investigator if such activity may jeopardize a patent application, an existing patent, or other proprietary rights. G1 Therapeutics shall determine order of authorship of any publication combining all clinical results of this study.

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17. APPENDICES

17.1. Clinical Laboratory Tests

- The timing and laboratory tests detailed in Schedule of Assessments (Table 6) will be performed by a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 7 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations

Table 13: Protocol-Specified Safety Laboratory Assessments

Laboratory Assessment	Parameters		
Hematology	WBC	Hemoglobin	Absolute neutrophil count
	Platelets	Lymphocytes	Hematocrit
Serum Chemistry	Blood Urea Nitrogen (BUN) or Urea	Serum Creatinine	Bicarbonate
	Aspartate Aminotransferase (AST)	Alanine Aminotransferase (ALT)	Calcium
	Potassium	Sodium	Chloride
	Glucose	Total Protein	Albumin
	Alkaline phosphatase	Total Bilirubin	
Other Tests	Serum or urine human chorionic gonadotropin (hCG) pregnancy test (for WOCBP only)		

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

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

17.2.1. Definition of AE

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

17.2.2. Definition of SAE

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

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

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

AE and SAE Recording

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

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

Assessment of Intensity

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

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

AE and SAE Recording

Assessment of Causality

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

Follow-up of AEs and SAEs

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

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

17.2.4. Reporting of SAEs

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

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

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

17.3. Contraceptive Guidance and Collection of Pregnancy Information

WOCBP Definition

Woman of Childbearing Potential

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

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

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

1. Premenarchal

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

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

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

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

Contraception Guidance

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

- Male patients: Males must be surgically sterile prior to Screening with appropriate documentation (absence of sperm in ejaculate 6 months after procedure) or have a female partner(s) who is either postmenopausal, surgically sterile, or using 2 forms of concurrent contraception as defined below. In addition, males must also refrain from sperm donation during the study and utilize a barrier method with intercourse during and for 3 months following discontinuation of treatment.

- Female patients: All females of childbearing potential must have a negative serum β-hCG test result at Screening, on Day 1 of each cycle, and at the End of Treatment Visit.

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

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

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

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator or designee will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to males who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator or designee will record pregnancy information on the Pregnancy – Initial Report Form and submitted to G1 Therapeutics PVG or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. The Pregnancy – Follow-up Report Form should be used to report information on the status of the mother and child and will be forwarded to G1 Therapeutics PVG or designee. Generally, the follow-up will be no longer than 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

  Contact for Pregnancy reporting:

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

Female Patients who become pregnant

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

  Contact for Pregnancy reporting:

  G1 Therapeutics Pharmacovigilance

  Email: safetyreporting@g1therapeutics.com

  Fax: +1-984-285-7131

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

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

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

- 10 mm by CT or MRI (with a scan slice thickness of no greater than 5 mm)
- Measurable lymph nodes must be ≥15 mm on the short axis by CT or MRI (with a scan slice thickness of no greater than 5 mm); only the short axis is to be measured at baseline and follow-up.
- Bone lesions: Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Cystic lesions representing cystic metastases that meet the definition of measurability described above can be considered measurable lesions. If present, noncystic lesions should be selected as target lesions for this study.
- A tumor lesion that has been previously irradiated may be considered measurable if unequivocal growth of the lesion has been demonstrated.

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

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

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

Evaluation of Target Lesions

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

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

Appearance of New Lesions

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

Timepoint Response

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

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

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

[a] Unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

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