Protocol Title: A Phase 2 Randomized, Double-blind, Clinical Trial of Trilaciclib versus Placebo in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with Docetaxel in the 2nd/3rd Line Setting (PRESERVE 4)

Protocol Number: G1T28-210

Compound: Trilaciclib for Injection, 300 mg/vial

Study Phase: 2

Study Name: PRESERVE 4

Sponsor Name: G1 Therapeutics, Inc.

Legal Registered Address: G1 Therapeutics, Inc.
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Regulatory Agency Identifier Numbers: IND: 154630
EudraCT: 2021-000186-32

Approval Date: 20 May 2021 (Version 2.0)

Original Protocol: 01 Feb 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 G1T28-210 dated 20 May 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.

[redacted]

[redacted]

Date

G1 Therapeutics, Inc.

INVESTIGATOR'S AGREEMENT

Clinical Study Protocol G1T28-210: A Phase 2 Randomized, Double-blind, Clinical Trial of Trilaciclib versus Placebo in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with Docetaxel in the 2nd/3rd Line Setting (PRESERVE 4)

Protocol Amendment 1 (Version 2.0) Issue Date: 20 May 2021

Original Protocol (Version 1.0) Issue Date: 01 Feb 2021

I have read the G1T28-210 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Principal Investigator Signature	Date
Principal Investigator Name	Institution

1. SYNOPSIS

Name of Sponsor/Company: G1 Therapeutics, Inc.		
Name of Investigational Product: Trilaciclib for Injection, 300 mg/vial		
Name of Active Ingredient: Trilaciclib dihydrochloride (hereafter referred to as trilaciclib) (G1T28)		
Protocol Number: G1T28-210	**Phase:** 2	**Country:** Worldwide
Title of Study: A Phase 2 Randomized, Double-blind, Clinical Trial of Trilaciclib versus Placebo in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with Docetaxel in the 2nd/3rd Line Setting (PRESERVE 4)		
Study center(s): Approximately 60 centers		
Study period: Estimated date first patient enrolled: 2Q2021 Estimated date last patient completed: 1Q2024		
Objectives: **Primary:** To assess the effect of trilaciclib administered prior to docetaxel compared with placebo administered prior to docetaxel on overall survival (OS) in patients with metastatic NSCLC receiving docetaxel in the 2nd or 3rd line. **Study Design:** This is a randomized, double-blind, placebo-controlled, global, multicenter, Phase 2 trial evaluating the effect of trilaciclib compared with placebo on OS in metastatic NSCLC patients receiving docetaxel in the 2nd or 3rd line setting. Patients must have documented disease progression during or after one or two lines of systemic therapy for recurrent or metastatic NSCLC. Prior treatment must have included, either in the same line or as separate lines of therapy: 1) a maximum of 1 line of platinum-containing chemotherapy for recurrent/metastatic disease and 2) a maximum of 1 line of a locally approved/authorized programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb) containing regimen for recurrent/metastatic disease. Patients will be randomly assigned (1:1) to receive trilaciclib or placebo intravenously (IV) prior to docetaxel on Day 1 of each 21-day cycle. There will be 2 stratification factors for randomization: Country and Eastern Cooperative Oncology Group (ECOG) performance status (0-1 versus 2). Within each country, patient randomization will be stratified by ECOG performance status (0-1 versus 2). Study drugs will be administered as follows: • Trilaciclib (240 mg/m^2) or placebo – administered as a 30-minute IV infusion no more than 4 hours prior to chemotherapy on each day chemotherapy is administered. • Docetaxel 75 mg/m^2 – IV, Day 1 The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of randomization for the first patient and completes at the Post-Treatment visit for the last patient. The first Survival Follow-up assessment should occur ~2 months after the last dose of study drug. The patient may continue to receive treatment on study until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever		

occurs first. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons.

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

Methodology:

Sample Size Justification:

The sample size is determined to support the primary objective of the study. That is, to evaluate the effect of trilaciclib compared to placebo on the OS of patients with metastatic NSCLC receiving docetaxel in the 2nd/3rd line setting. A total of 104 deaths will be required to achieve 85% power to detect a hazard ratio (HR) of 0.55 in OS at a 2-sided significance level of 0.05. A HR of 0.55 corresponds to a median OS of 16.5 months for the trilaciclib group assuming a median OS of 9.1 months for the placebo group (Garon, 2014). With a 12-month enrollment period and a 30-month study duration (after the first patient is randomized), a total of 146 patients are required for randomization at a 1:1 ratio to trilaciclib or placebo. This sample size has taken into consideration an interim analysis for OS at the information fraction of 0.70 using the O'Brien-Fleming method for α-spending to ensure strong control of Type I error rate at 1-sided 0.025 between the interim and the final analysis for OS. In the sample size calculation, it is also assumed that about 5% of patients are lost-to-follow-up during the 30--month study duration.

Number of patients (planned):

Approximately 146 patients with NSCLC 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 histologically or cytologically-confirmed metastatic NSCLC. Patients of any histology appropriate for treatment with docetaxel in the 2nd/3rd line will be eligible. Patients must have documented disease progression during or after treatment with platinum-based chemotherapy and a locally approved/authorized PD-1/PD-L1 inhibitor. Patients should not have been previously treated with docetaxel or with therapy targeted to driver mutations. Measurable or non-measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 is permitted as is ECOG performance status of 0 to 2. At the time of providing informed consent, a formalin-fixed paraffin-embedded (FFPE) tumor specimen (from archival or fresh biopsy) with an associated pathology report documenting NSCLC must be available to send to Sponsor, within the timeframe specified, for planned retrospective biomarker analyses.

Investigational product, dosage and mode of administration:

On Day 1 of each 21-day cycle, a dose of trilaciclib 240 mg/m^2 diluted in 250 mL of dextrose 5% in water or sodium chloride solution 0.9% will be administered as a 30-minute IV infusion no more than 4 hours prior to docetaxel administration.

Duration of treatment:

Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurs first.

Reference therapy, dosage and mode of administration:

On Day 1 of each 21-day cycle, a dose of placebo (250 mL of dextrose 5% in water or sodium chloride solution 0.9%) will be administered by IV infusion over approximately 30 minutes no more than 4 hours prior to docetaxel administration.

On Day 1 of each 21-day cycle, docetaxel will be administered IV in accordance with the prescribing information and institutional guidelines.

Criteria for evaluation:

Efficacy:

Antitumor efficacy will be assessed by OS, PFS, objective response rate (ORR), and duration of objective response (DOR). Tumor response criteria will be based on RECIST v1.1.

Myelopreservation efficacy will be assessed based on hematology assessments, myelosuppression-related adverse event (AE) details, dose reductions/delays and supportive care interventions (including transfusions).

Safety:

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

PROs:

Patient-reported outcomes (PROs) will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-LC13 with supplemental weight loss item (EORTC IL118), Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), and 5-level EQ-5D (EQ-5D-5L).

Pharmacodynamics:

Pharmacodynamics will be assessed using peripheral blood to evaluate potential markers of response and resistance, including immune effects.

Statistical methods:

Data will be summarized by treatment group. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, standard deviations, medians, 25% and 75% percentiles, and minimum and maximum values.

Stratification factors and factors used in statistical models:

There are two stratification factors for randomization: country and ECOG performance status (0-1 versus 2). Within each country, patient randomization will be stratified by ECOG performance status (0-1 versus 2). A randomization schema will be in place to ensure the best possible balance of treatment assignment within each stratum produced by these stratification factors. Countries will be grouped into the factor of "region" with 3 components: United States (US), Europe, and Asia. The factor "region" will be used instead of "country" in the statistical analysis models to account for regional differences in clinical practice.

Analysis population

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

The response evaluable (RE) population will include patients in the ITT population who have a measurable lesion (target lesions) at the baseline tumor assessment, and either (i) have at least 1 post-dose tumor assessment, or (ii) do not have post-dose tumor assessment but have clinical progression as noted by the Investigator, or (iii) have died due to disease progression before their first post-dose tumor scan. RE population will be the primary analysis set to evaluate tumor response and the data will be analyzed based on the randomly assigned treatment.

The safety population includes all randomized patients who received at least one dose of study drug. Analyses conducted on the safety population will be based on the actual treatment received. All safety analyses will be conducted using the safety population.

The pharmacokinetic (PK) population will include all patients who received at least one dose of study drug and had evaluable PK data.

Statistical analysis methods for primary and secondary endpoints

Analysis for Primary Endpoint

The primary endpoint OS is defined as the time (months) from the date of randomization to the date of death for patients who died in the study due to any cause, and the time to the last contact date known to be alive for those who survived as of the data cutoff date for the interim OS analysis or as of the date for the final database lock (censored cases). Patients lacking data beyond the date of randomization will have their survival time censored at the date of randomization. The targeted number of deaths for the final analysis is 104 and the analysis for OS is event-driven.

Treatment effect on OS will be primarily evaluated using a stratified log-rank test controlling for the stratification factors of region (US, Europe, or Asia), and ECOG performance status (0-1 versus 2). Unless otherwise specified, ECOG status information as entered in the Interactive Web Response System (IWRS) at the time of randomization will be used as the factor for this and all other stratified analyses. The magnitude of the treatment effect, HR (trilaciclib versus placebo), will be estimated using a Cox proportional hazard model with the same factors as included in the stratified log-rank test. Additionally, the Kaplan-Meier plots will be generated, and the median, 25% and 75% percentile of OS will be estimated using the Kaplan-Meier method with their corresponding 95% confidence interval calculated based on the method by Brookmeyer and Crowley (1982) for each treatment group. The analyses for OS will be performed on the ITT population.

Interim Analysis for OS

An interim analysis of OS will be conducted at the 70% information fraction, that is, when 73 deaths are observed. The timing of the interim analysis is estimated to be approximately 19 months after the first patient is randomized in the study. To perform the interim analysis, the database will be locked. If the interim OS analysis result by the stratified log-rank test is positive as determined by the pre-specified statistical criterion, the study will be stopped for success and the results from the interim OS analyses are considered to be final. If the interim OS analysis result does not meet the criterion of success, the study will continue until a total of 104 deaths are observed. At that time, the study database will be locked to perform the final OS analysis. It is estimated that it will take approximately 30 months after the first patient is randomized in the study to reach the total targeted number of deaths in this study.

Analysis for secondary anti-tumor efficacy endpoints

PFS

PFS is defined as the time (months) from date of randomization until date of documented radiologic 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 time of performing the analysis, PFS will be calculated per censoring rules detailed in the Statistical Analysis Plan (SAP).

Per literature, the expected median PFS for patients receiving docetaxel is 3 months (Garon, 2014). Assuming trilaciclib can achieve a treatment effect of HR of 0.60, it is estimated that at the time of performing the OS interim analysis, 86% of patients would have a radiographic-determined disease progression or died. Therefore, the analysis for PFS will be conducted at the time when the OS interim analysis is conducted since the PFS events are considered mature. Treatment effect on PFS will be evaluated using the stratified log-rank test controlling for the two stratification factors. A Cox proportional hazard model with the same terms as in the stratified log-rank test will be used to estimate the HR between the 2 treatment groups (trilaciclib versus placebo) for PFS along with its 95%

confidence interval. In addition, the Kaplan-Meier plots will be produced, and the median, 25% and 75% percentile of PFS will be estimated using the Kaplan-Meier method with their corresponding 95% confidence interval calculated based on the method by Brookmeyer and Crowley (1982) for each treatment group. PFS will be analyzed on the ITT population.

Tumor Response

Objective response is defined as achieving either complete response (CR) or partial response (PR) per RECIST v1.1. The ORR along with its exact 95% two-sided confidence interval using the Clopper-Pearson method will be computed for each treatment group. The treatment effect on ORR will be evaluated using a stratified Cochran–Mantel–Haenszel (CMH) method to account for the two stratification factors. The adjusted proportion difference (trilaciclib minus placebo) and its 95% confidence intervals will be calculated using CMH weight. ORR will be analyzed on the Response Evaluable patient population.

DOR is the time (months) between the date 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 12.4.6.2.2. The median, 25% and 75% percentile of DOR will be estimated using the Kaplan-Meier method with their corresponding 95% confidence interval calculated based on the method by Brookmeyer and Crowley (1982) for each treatment group.

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 by treatment group 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 (SOC) and preferred term (PT) using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The severity (toxicity grades 1-5) will be summarized by SOC, PT and CTCAE grade, as appropriate. In the tabulation of severity and causality for an AE, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be used. Concomitant medications, as well as prior and subsequent anticancer therapies, will be coded to Anatomical Therapeutic Classification (ATC) using the World Health Organization-Drug Dictionary (WHO-DD) and summarized by treatment group.

For laboratory assessments, vital signs, and ECG intervals, observed values and changes from baseline will be summarized by treatment group. For serum chemistry AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0 by Investigators. AEs overall, AEs related to each study drug, AEs leading to study drug discontinuation or dose modifications, and trilaciclib AEs of special interests (AESIs) will be summarized by SOC, PT and CTCAE grade, as appropriate. For laboratory assessments, vital signs, and ECG intervals, observed values and changes from baseline will be summarized by treatment group. For serum chemistry and hematology laboratory parameters, clinical labs will be characterized according to CTCAE toxicity grade from 1 to 5, 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.

Pharmacokinetic/Pharmacodynamic Analyses

Analyses may be performed to examine the relationship(s) between exposure to trilaciclib and pharmacodynamic endpoints or other efficacy and safety endpoints.

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

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3. LIST OF ABBREVIATIONS

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

Table 1: Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
aRR	adjusted relative risk
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BED	biologically effective dose
β-hCG	beta human chorionic gonadotropin
BICR	blinded independent central review
BMI	body mass index
BOR	best overall response
BSA	body surface area
BSEP	bile salt export pump
CAP	College of American Pathologists
CBC	complete blood count
CD	cluster of differentiation
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CIM	chemotherapy-induced myelosuppression

Abbreviation	Definition
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPS	combined positive score
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CYP	cytochrome P450
D5W	dextrose 5% in water
DC	dendritic cell
DCAF	d-type cyclin activating features
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of objective response
DSN	duration of sever neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Module
EORTC IL118	European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Module with supplemental weight loss item
EOT	End of Treatment
E/P	etoposide plus carboplatin
E/P/A	cisplatin, etoposide and atezolizumab
ES-SCLC	extensive stage SCLC
EQ-5D-5L	5-level EQ-5D

Abbreviation	Definition
EQ-VAS	EQ visual analogue scale
ER	estrogen receptor
ESA	erythropoiesis stimulating agent
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FN	febrile neutropenia
FSH	follicle stimulating hormone
G_1	gap 1 phase of the cell cycle
G_2	gap 2 phase of the cell cycle
G1T28	trilaciclib; formerly G1T28-1
GC	gemcitabine and carboplatin
GC therapy	gemcitabine and carboplatin on Days 1 and 8 of 21-day cycles
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
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
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitors
IEC	independent ethics committee

Abbreviation	Definition
IFN	interferon
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	International Normalized Ratio
IP	intraperitoneal
IRB	institutional review board
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
Ki	inhibition constant
LFT	liver function test
M	mitosis
mAb	monoclonal antibody
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
MDR1	p-glycoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MOA	mechanism of action
MRI	magnetic resonance imaging
MRP1 or 2	multidrug resistance protein 1 or 2
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
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

Abbreviation	Definition
PCS	potentially clinically significant
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDX	patient derived xenografts
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	preferred term
PTFE	polytetrafluorethylene
PVG	pharmacovigilance
QTcF	QT corrected using Fridericia's formula
Rb	retinoblastoma protein
RB	retinoblastoma gene
RBC	red blood cell
RE	Response Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ROS oncogene 1
RP2D	recommended Phase 2 dose
S	synthesis phase of the cell cycle
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SOC	system organ class
SN	severe neutropenia
SUSAR	suspected unexpected serious adverse reactions

Abbreviation	Definition
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TIM3	T-cell immunoglobulin and mucin domain 3
TNBC	triple-negative breast cancer
T_{reg}	regulatory T cells
TTCD-fatigue	Time to confirmed deterioration of fatigue
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

4. INTRODUCTION

4.1. Lung Cancer

Worldwide, there were more than 2 million cases of lung cancer and 1.75 million lung cancer related deaths in 2018 (WHO, 2020). The American Cancer Society estimates that in 2020, ~135,000 of those lung cancer deaths will occur in the US alone (American Cancer Society, 2020). Approximately 84% of these patients will be diagnosed with non-small cell lung cancer (NSCLC) and almost 70% will present with locally advanced or metastatic disease (ASCO, 2020; Little, 2007). Historically, treatment in the metastatic setting has been driven almost exclusively by the use of systemic chemotherapy. However, in the last ten to twenty years, a greater understanding of the pathways that dictate tumor response and the advent of multiple targeted therapies has changed the landscape of treatment options significantly. Lung tumors are routinely tested for the presence of specific driver mutations (e.g., epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], BRAF, and cROS- oncogene 1 [ROS1]), that predict a favorable response to targeted tyrosine kinase inhibitors (Kalemkerian, 2018). As many as 50% to 64% of patients have been identified as having a targetable genetic alteration and those that receive treatment have better outcomes (Kris, 2014; Barlesi, 2016).

For those patients without a targetable genetic alteration, treatment options have also changed considerably. Though systemic therapy remains an important component of treatment in this context, the advent of immunotherapy has significantly improved outcomes for this patient population. Multiple randomized trials, in both squamous and non-squamous histologies, have established that overall survival (OS) is improved with the addition of programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibitors (Spigel, 2019; Reck, 2016; Gandhi, 2018; Paz-Ares, 2018). Those with high levels of PD-L1 expression typically receive pembrolizumab or atezolizumab monotherapy in the first line followed by platinum-based chemotherapy in order to maximize treatment response and minimize toxicity. Those with a higher burden of disease requiring more aggressive initial treatment or with lower levels of PD-L1 expression typically receive immunotherapy in combination with a platinum-based chemotherapy doublet.

Despite these improvements in the therapy for metastatic NSCLC, the majority of patients ultimately progress during or after treatment with immunotherapy and platinum-based chemotherapy. Management of this pretreated patient population is challenging and treatment options are limited to single agent chemotherapies such as docetaxel, pemetrexed (for those with non-squamous histology), and gemcitabine (Shepherd, 2000; Fossella, 2010; Gridelli, 2004; Hanna, 2004; Anderson, 2000). The clinical trials that established these treatment options predated immunotherapies and robust data for individual agents is often lacking. The high-level evidence that does exist demonstrates a limited impact of 2nd line therapy on treatment outcomes. For example, in a study where 1,253 patients were treated with docetaxel plus or minus the VEGFR2 inhibitor ramucirumab following progression on platinum-based- chemotherapy, survival was significantly improved with the addition of ramucirumab, but the clinical benefit was only 1.5 months (hazard ratio [HR] 0.86, p=0.023) (Garon, 2014).

In contrast, the large Phase 3 studies evaluating the addition of immunotherapy in the first line consistently demonstrated large treatment effects (HRs ~0.5-0.6) that were both statistically

significant and highly clinically meaningful (Spigel, 2019; Reck, 2016; Gandhi, 2018; Paz-Ares, 2018). In an effort to translate these early successes to later lines of therapy, numerous ongoing Phase 3 studies are evaluating the continuation of PD-1/PD-L1 inhibitors (following progression on the same) in combination with kinase inhibitors hypothesized to synergistically illicit an ongoing immune response. However, the mechanisms of immune checkpoint inhibitor (ICI) resistance are complex and 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, 2019; Barrueto, 2020; Jenkins, 2018; Fares, 2019; Borcherding, 2018; Gidel, 2018). Novel therapies, whose mechanisms broadly target these ICI mechanisms of resistance, including CDK4/6 inhibition, could be particularly valuable following disease progression on currently clinically available immunotherapies.

In addition to the need for therapies that more effectively extend overall survival, patients treated in the metastatic setting are particularly vulnerable to the chemotherapy-induced myelosuppression (CIM) and health-related quality of life impacts associated with extensive systemic therapy. CIM is a significant issue in cancer treatment; patients with myelosuppression are more likely to experience infections, sepsis, bleeding, and fatigue, often leading to the need for hospitalizations, hematopoietic growth factor support, transfusions (red blood cells [RBCs] and/or platelets) and even death (Caggiano, 2005; Gustinetti, 2016; Bodey, 1966; Li, 2016). Moreover, CIM commonly leads to dose reductions and delays, which limit therapeutic dose intensity and can compromise the anti-tumor efficacy benefits of chemotherapy. Furthermore, existing supportive care interventions for CIM are generally used after the onset of symptoms, only address the deficiency of a single blood cell lineage and carry their own set of risks and limitations. Introducing a therapy that can protect the hematopoietic stem and progenitor cells (HSPCs) of the host from CIM has the potential to maximize the anti-tumor activity of the chemotherapy while minimizing the consequences to the patient of chemotherapy-induced cellular damage.

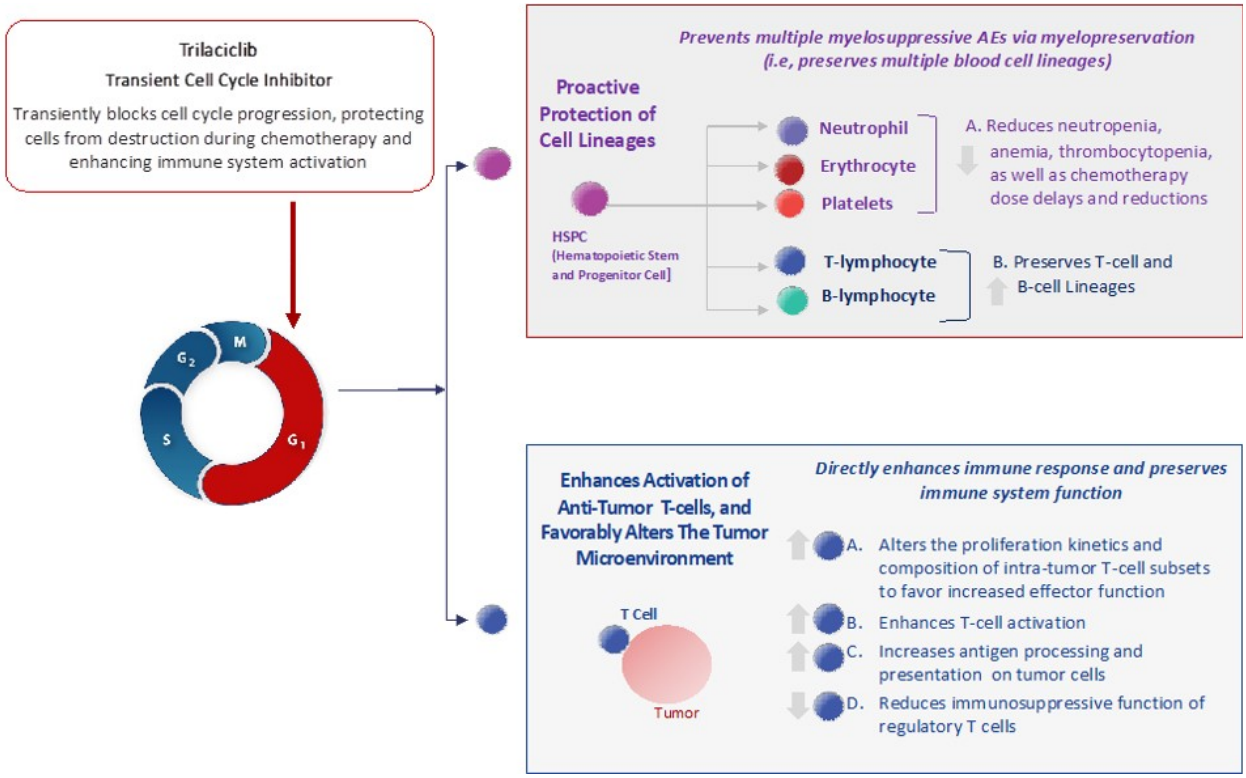
In summary, though immunotherapy has markedly improved the treatment of metastatic NSCLC, options following disease progression on these therapies remain limited. An alternative therapy that extends the duration of OS without significant additive toxicity, while concurrently decreasing myelosuppression and improving quality of life, would be a welcome addition in this heavily pretreated and often clinically fragile patient population. Therefore, further evaluation of trilaciclib in this area of high unmet medical need is warranted.

4.2. Study Rationale

Trilaciclib is a highly potent and selective, reversible, cyclin-dependent kinase (CDK) 4/6 inhibitor that preserves HSPCs as well as immune system function during chemotherapy (myelopreservation) 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 and ICIs (He, 2017; Bisi, 2016; Lai, 2020). 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

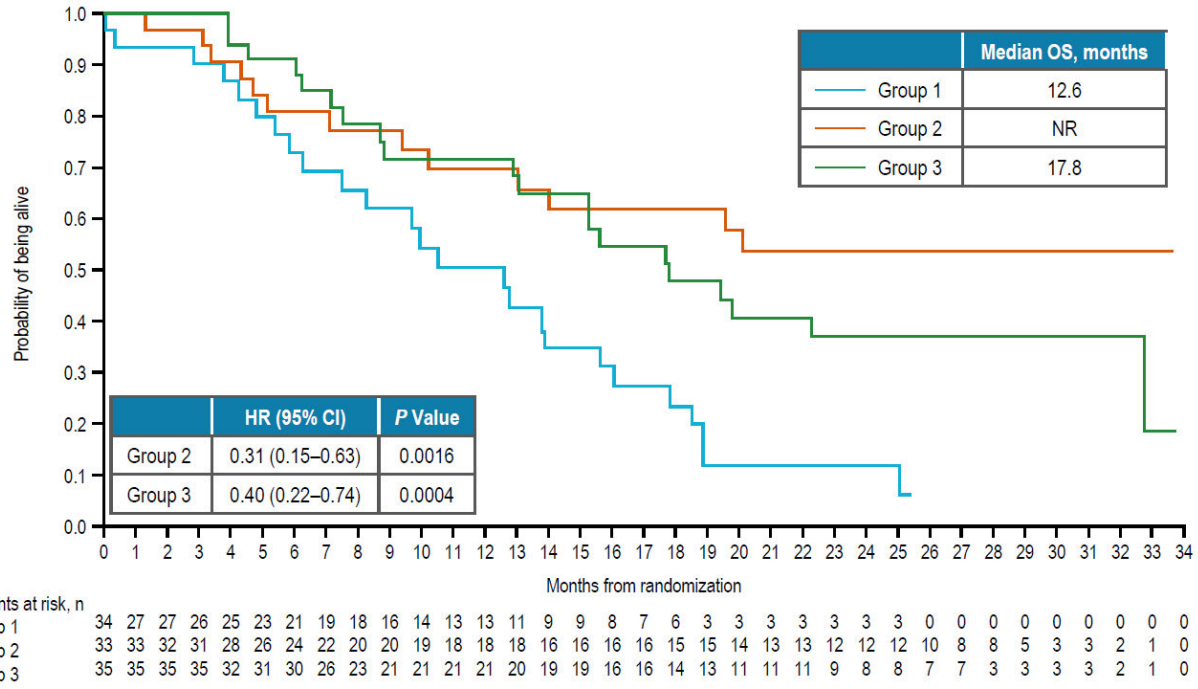
The use of trilaciclib for patients with triple-negative breast cancer (TNBC) was evaluated in Study G1T28-04, a global, multicenter, randomized, open-label, Phase 2 clinical trial to evaluate the safety, efficacy, and pharmacokinetics (PK) of trilaciclib administered prior to gemcitabine/carboplatin (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 small cell lung cancer (SCLC), where trilaciclib development has focused on myelopreservation benefits (Section 4.2.8.1). Three randomized, double-blind, Phase 2 clinical trials (G1T28-02, G1T28-03 and G1T28-05) 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 (Section 4.2.8.1; Table 2; Weiss, 2019; Hart, 2019; Daniel, 2019). While the benefit in chemotherapy-induced myelosuppression in these studies was striking, these myelopreservation benefits were observed in the setting of only minor improvements in progression-free survival (PFS) and OS as evidenced by HRs <1.0 in almost all clinical settings for trilaciclib compared with placebo.

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 versus not evaluable or 17.8 months in the two trilaciclib groups, HR: 0.31 [p=0.0016] and HR: 0.40 [p=0.0004], respectively; Figure 2) and by PFS (median PFS in control 5.7 months versus 9.4 months or 7.3 months in the two trilaciclib groups HR: 0.65 and 0.57, respectively; not statistically significant) (O'Shaughnessy, 2020; Tan, 2019). The clinically meaningful anti-tumor efficacy results observed in G1T28-04 were noted across both of the trilaciclib treatment groups and in the context of a control group with survival reflective of published literature.

Figure 2: G1T28-04: Overall Survival – Kaplan-Meier Curve (ITT Analysis Set)



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NR=not reached.

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 2 and 9 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.

The impact on OS was consistent across subgroups, including predictors of immune response. Approximately 57.6% of the available tumor samples in G1T28-04 were considered PD-L1 positive (Ventana SP142 assay), and though larger in the PD-L1 positive population, the benefit of adding trilaciclib extended to both PD-L1 positive and negative cohorts (Table 4).

The translation of these anti-tumor efficacy findings to other tumor types is predicted to be primarily driven by the tumor type, chemotherapy type and host, i.e., (1) the tumor must be sufficiently immunogenic and sensitive to the host cytolytic efforts as to see improvement in anti-tumor endpoints like OS, (2) the chemotherapy should promote immune activation, and (3) the host must be able to mount an effective cytolytic response against the tumor. In the SCLC trials, the addition of trilaciclib to the standard of care therapies provided modest improvement, to neutral effects, on measures of anti-tumor efficacy including objective response rate (ORR), PFS and OS. These results are not surprising considering that SCLC is one of the most aggressive solid tumors and is not particularly immunogenic or sensitive to immune modulation (Wang, 2019).

In contrast, NSCLC has been extensively documented as sensitive to immune modulation with multiple established immunotherapy treatment options in the early lines of treatment for metastatic NSCLC (Spigel, 2019; Wang, 2019; Reck, 2016; Gandhi, 2018; Paz-Ares, 2018). This highly responsive NSCLC immune milieu and the novel trilaciclib immune activating effects described below provide a strong rationale to evaluate the efficacy of trilaciclib in patients with previously treated NSCLC.

4.2.2. Rationale for Immunogenicity of NSCLC Tumor Type and Docetaxel Chemotherapy

While NSCLC has been recognized as having an immunosuppressive tumor microenvironment through high numbers of regulatory T cells (T_{reg}) directly inhibiting T-cell proliferation (Woo, 2001; Woo, 2002), tumor-infiltrating cluster of differentiation (CD)8^+ T cells with increased PD-1 expression (Zhang, 2010), and downregulation of major histocompatibility complex (MHC) class I/tumor antigen expression (Korkolopoulou, 1996), results from numerous trials evaluating immunotherapeutic agents, including immune checkpoint inhibitors, have demonstrated the efficacy of this approach in NSCLC (Spigel, 2019; Reck, 2016; Gandhi, 2018; Paz-Ares, 2018).

A number of immune correlates of clinical outcome in patients with NSCLC have been identified providing clinical evidence for immune system involvement in NSCLC. High levels of infiltrating $CD8^+$, $CD4^+$, $CD3^+$ T cells as well as higher densities of mature dendritic cells (DCs) have been associated with improved survival (Wing, 2008; Chen, 2012). Conversely, the number of T_{reg} cells as well as PD-L1 expression in NSCLC tumors have been shown to be independent predictors of reduced survival or unfavorable prognosis in patients with NSCLC, respectively (Petersen, 2006; Shimizu, 2010; Mu, 2011).

In addition to the inherent immunogenicity associated with NSCLC, docetaxel has demonstrated an ability to enhance the sensitivity of tumors to immune-mediated cell death (Hodge, 2013). In particular, immune modulating effects on the tumor stroma have been noted (Opzoomer, 2019). *In vivo*, docetaxel has been shown to induce selective cell death in myeloid-derived suppressor cells known to contribute to immune suppression while simultaneously promoting differentiation of this cell type towards a pro-inflammatory phenotype (Kodumudi, 2010). Lastly, docetaxel has

been shown to decrease T_{reg} cells in patients with non-small cell lung cancer (Li, 2014). Taken together, these data suggest docetaxel may lead to immune activation in NSCLC and further the potential benefit of trilaciclib.

4.2.3. 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 ES-SCLC, flow cytometry and T cell receptor (TCR) immunosequencing data revealed that patients receiving trilaciclib had an increased ratio of total and activated $CD8^+$ 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 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 ES-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 in G1T28-04, 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, when patients were stratified above or below median Simpson clonality at baseline, there was an improvement among patients receiving trilaciclib. In addition to a decrease in Simpson clonality, responders receiving trilaciclib prior to GC had more newly detected expanded T-cell 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).

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. Further, there appear to be several immune based mechanisms through which this effect can be mediated including neoantigen presentation and T cell activation and function.

4.2.4. Rationale for Trilaciclib following Progression on Immunotherapy

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 (MHC class I), enhancing T cell clonality and tumor infiltration, inhibiting regulatory T cell proliferation, decreasing T cell exhaustion markers (PD-1, cytotoxic T-lymphocyte associated protein 4 [CTLA-4], and T-cell immunoglobulin and mucin domain 3 [TIM3]), stabilizing expression of PD-L1 on tumor cells, promoting dendritic cell migration, and increasing T effector cell function through high interferon [IFN] gamma production (Chaikovsky and Sage, 2018; Deng, 2018; Goel, 2017; Schaer, 2018; Lai, 2020; Bonelli, 2019; Teh and Aplin, 2019).

Multiple ongoing trials in this setting, i.e., following disease progression on platinum-based chemotherapy and immunotherapy, are evaluating additional checkpoint inhibitor therapy, but in combination with a partner hypothesized to promote an ongoing immune response. However, as described above, multiple mechanisms of resistance can develop following treatment with immunotherapy and novel agents that exploit multiple or alternative pathways may be preferred. In addition to documented anti-tumor immune modulating effects alone and in combination with checkpoint inhibitors, trilaciclib has translated these effects to improved survival in the TNBC setting and belongs to a class of agents with a diverse repertoire of immune-modulating effects. Overall, these data suggest that patients may benefit from trilaciclib after progressing on ICI treatment.

4.2.5. Rationale for Myelopreservation

Trilaciclib has shown well-documented improvement in myelosuppression outcomes that could provide a substantial benefit to patients receiving docetaxel. In the REVEL trial, 39% of patients receiving docetaxel alone experienced grade 3 or greater neutropenia with 10% experiencing febrile neutropenia (FN) (Garon, 2014). In addition, 6% of patients experienced Grade 3 or greater anemia. Patients treated for SCLC with trilaciclib had marked reductions in the occurrence of these endpoints, required less supportive care, and experienced enhanced quality of life (Table 2).

4.2.6. Rationale for Combination with Docetaxel

Following progression on chemotherapy and immunotherapy, single-agent chemotherapy is the most common standard of care. As there is limited high-quality data for any specific agent in the modern era, several options can be utilized. However, single-agent docetaxel, with activity in both squamous and non-squamous histologies, is commonly utilized in clinical practice and as the reference standard in metastatic NSCLC clinical trials.

Ramucirumab in combination with docetaxel is also approved for the treatment of metastatic NSCLC following disease progression on or after platinum-based chemotherapy. This approval was based on a Phase 3 study that revealed a 1.5-month improvement in survival with the addition of ramucirumab. However, the rate of grade 3 or greater treatment-emergent adverse events increased from 71% to 79%. Furthermore, this small benefit occurred prior to the widespread use of immunotherapy. It is unclear if the same benefit would be seen in patients treated with today's standard of care. As a result, National Comprehensive Cancer Network (NCCN) guidelines list both the combination and docetaxel alone as potential treatment options in this clinical setting and utilization is at the discretion of the individual provider. Because there are no mature data available evaluating the combination of trilaciclib and a taxane containing regimen, the risks of also incorporating ramucirumab were felt to outweigh the small associated benefits.

Trilaciclib has been successfully combined at the recommended Phase 2 dose with most major chemotherapy classes other than microtubule inhibitors. In three randomized, controlled, Phase 2 studies in SCLC patients, the combination resulted in consistent improvements in chemotherapy-induced myelosuppression across multiple lineages. Even in the TNBC trial where the addition of trilaciclib to gemcitabine/carboplatin did not improve neutropenia-based myelopreservation endpoints, rates of adverse events were comparable despite patients on trilaciclib receiving almost double the number of chemotherapy cycles. There is no evidence to suggest that a

different result would be expected from the combination of trilaciclib with taxane based chemotherapy.

Preclinical *in vivo* studies evaluating trilaciclib in combination with paclitaxel or docetaxel utilizing a clinically relevant dose administration schedule support the safety of this combination. In addition, there are at least 4 clinical studies combining chronically dosed oral CDK4/6 inhibitors (palbociclib, ribociclib) with taxane-based chemotherapy. Two of those studies have reported acceptable early safety results in combination with standard clinical doses of paclitaxel and docetaxel (Lewis, 2018; Clark, 2019). In both of these studies, patients received multiple doses of oral CDK4/6 inhibitors (known to cause neutropenia). In contrast, trilaciclib is an IV CDK4/6 inhibitor dosed only prior to chemotherapy. Finally, trilaciclib is being evaluated in an ongoing Phase 2 study in combination with paclitaxel in the neoadjuvant breast cancer setting.

4.2.7. Summary of Nonclinical Data

A summary of the trilaciclib nonclinical data is presented in the trilaciclib Investigator's Brochure (IB).

Nonclinical data related to docetaxel are provided in the local prescribing information.

4.2.7.1. Pharmacology Studies

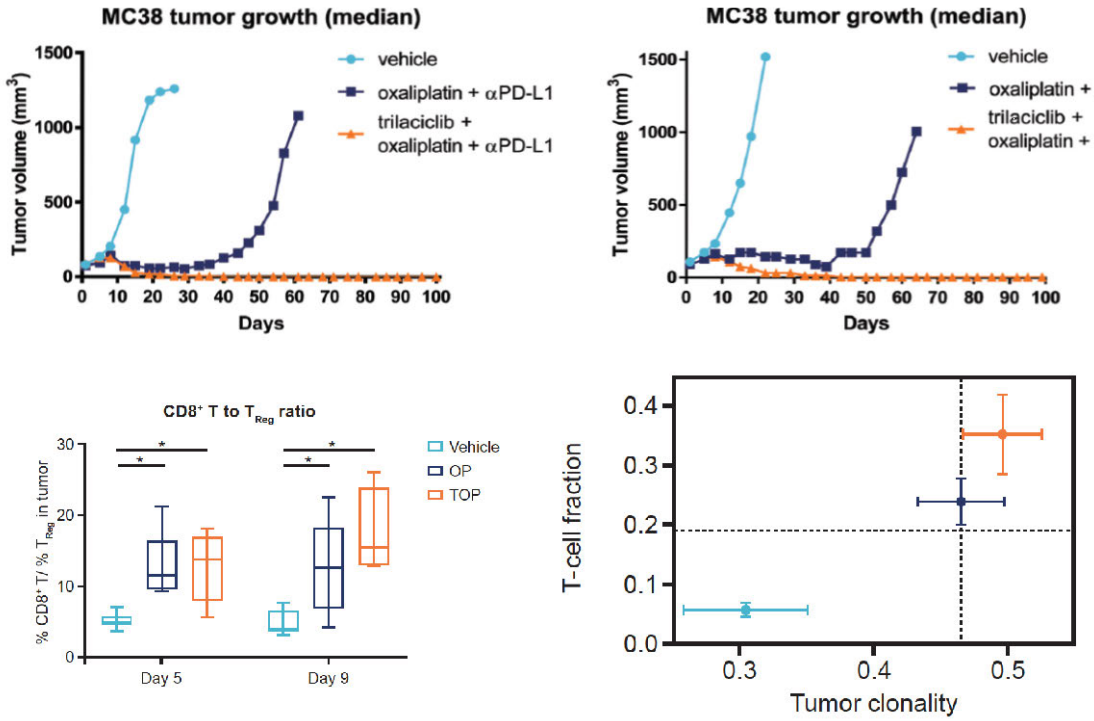
Through a structure-based design approach to optimize potency, selectivity, and drug metabolism and PK properties, G1 Therapeutics, Inc. identified trilaciclib as a highly potent inhibitor of CDK4 and CDK6 (half maximal inhibitory concentration [IC_{50}] values of 1 nM and 4 nM, respectively) that is highly selective for CDK4/Cyclin D1 versus cyclin-dependent kinase 2 (CDK2)/Cyclin E (>2500-fold selectivity). Trilaciclib also demonstrated reversible inhibition of CDK4/Cyclin D1, with an inhibition constant (Ki) 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 chemotherapy 5-fluorouracil (5-FU) that is highly myelosuppressive in mice, 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 has also shown that trilaciclib enhances immune activation and promotes anti-tumor immunity by differentially arresting cytotoxic and regulatory T-cell subsets followed by a faster recovery in cytotoxic T lymphocytes than in 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 3; 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 3: The Addition of Trilaciclib to Chemotherapy/Immune Checkpoint Inhibitor Treatment Enhances Efficacy Through T Cell Activation



(Upper right and upper left) Addition of trilaciclib to oxaliplatin and αPD-L1/ αPD-1combination therapy led to enhanced anti-tumor activity and durability of response in the MC38 tumor model (n=10–15 per treatment group). (Lower left) Transient G1 arrest led to changes in the proportion of intra-tumor T-cell subsets favoring effector T-cell function as measured by the ratio of $CD8^+$ T cells to Tregs (% $CD8^+$ T cells / % Tregs) in the $CD45^+$ population (n=5–8 tumors analyzed per treatment group and time point). (Lower right) Trilaciclib in combination with chemotherapy and ICI enhanced the gene signature of cytotoxic anti-tumor response. T-cell repertoire analyses of MC38 tumors from OP- or TOP-treated mice (n=5 per treatment group) on day 17, presented as median clonality score and TIL fraction (right panel). Error bars denote standard error, and dotted lines represent the median value for TIL fraction and clonality score. *p<0.05.

However, as a consequence of trilaciclib's MOA, there is a hypothetical risk that administration of trilaciclib prior to chemotherapy could decrease chemotherapy efficacy by pausing CDK4/6-dependent tumor cells in G_1 in the presence of chemotherapy; nonclinical data suggest this risk is not clinically significant. To understand why trilaciclib should not antagonize chemotherapy treatment, the baseline proliferation rates of HSPCs, bone marrow, and patient derived xenografts (PDX) were examined using flow cytometric analysis of the cell cycle. A bar graph depicting mean percentage of cells in synthesis phase of the cell cycle (S)/gap 2 phase of the cell cycle (G_2)/mitosis (M) demonstrates that there are a higher proportion of cells cycling in tumor cells when compared to bone marrow/HSPCs. Specifically, <4% of human HSPCs are cycling, while in breast tumors an average of ~40% of cells were cycling (Sorrentino, 2018).

These results illustrate why tumor cells are more susceptible to chemotherapy-induced damage compared to HSPCs, since chemotherapy treatment is predominantly effective in the S/G_2/M phases of the cell cycle.

To evaluate the impact of trilaciclib on chemotherapy anti-tumor efficacy in CDK4/6 dependent tumors, two different models were treated with chemotherapy and trilaciclib. MCF7 tumor-bearing mice, a well-established estrogen receptor (ER)+ CDK4/6 dependent breast cancer model, were treated with docetaxel (IV, 5 mg/kg) ± trilaciclib once weekly for three doses. Although weekly trilaciclib treatment caused some tumor growth inhibition, administering trilaciclib with docetaxel did not alter the effects of chemotherapy. Next, MDA-MB231 tumor-bearing mice were treated with daily trilaciclib (intraperitoneal [IP], 100 mg/kg) for 28 days to confirm CDK4/6 dependence. Continuous treatment with trilaciclib caused stable disease in MDA-MB231 tumor-bearing mice. MDA-MB231 tumor-bearing mice were then treated with eribulin (IV, 0.5 mg/kg) ± trilaciclib once weekly for three doses. Similar to the MCF7 model, the addition of trilaciclib to eribulin treatment did not impact chemotherapy efficacy (Sorrentino, 2018). These experiments demonstrate that transient CDK4/6 inhibition prior to chemotherapy (eribulin, docetaxel) does not antagonize the intended anti-tumor effects of the chemotherapy in these CDK4/6-dependent tumor models.

While there is emerging preclinical data demonstrating the efficacy of CDK4/6 inhibitors in combination with targeted therapy in NSCLC subpopulations (Freed, 2019; Gopalan, 2018; Haines, 2018; Knudsen, 2017), single agent efficacy has shown minimal benefit in the clinic (Goldman, 2020; Edelman, 2019; Gopalan, 2018; Patnaik, 2016). Furthermore, the available nonclinical *in vivo* data indicate combining chemotherapy with trilaciclib does not diminish the antitumor intended effects of the chemotherapy (data not shown, internal G1 data) as loss of CDK4/6 pathway function is correlated with increased tumor proliferation and improved tumor response to chemotherapy in a variety of cancer types (Socinski, 2009; Herschkowitz, 2008; Ertel, 2010; Witkiewicz, 2012). Lastly, applying a DNA signature analysis algorithm to the cBioportal dataset to characterize NSCLC tumors as CDK4/6 dependent, independent or indeterminate, only 7.4% of EGFR WT NSCLC lung tumor would be classified as CDK4/6 dependent (Gao, 2013; Cerami, 2012). Overall, preclinical and clinical data suggest that there is minimal risk that trilaciclib administered prior to docetaxel will induce a G1 arrest in the tumor cell with resultant antagonism of the intended efficacy effect of the chemotherapy.

4.2.7.2. Pharmacokinetic Studies

In vitro analyses of direct and time-dependent inhibition suggest that drug interactions based on inhibition of cytochrome P450 (CYP)1A2-, 2B6-, 2C8-, 2C9-, 2C19-, and 2D6-mediated metabolic pathways are unlikely at clinical doses, however, the studies do suggest that drug interactions based on trilaciclib-mediated inhibition of CYP3A4-mediated metabolic pathways are possible (see Section 4.2.8.1.1). 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 drug-drug interaction (DDI) based on inhibition of breast cancer resistance protein (BCRP)-, bile salt export pump (BSEP)-, organic anion transporter 1 (OAT1)-, organic anion transporter 3 (OAT3)-, organic anion transporting polypeptide 1B1 (OATP1B1)-, p

glycoprotein (MDR1)-, multidrug resistance protein 1 (MRP1)-, multidrug resistance protein 2 (MRP2)-, or organic anion transporting polypeptide 1B3 (OATP1B3)-mediated transport. However, in vitro, trilaciclib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1), multidrug and toxin extrusion 2-K (MATE2-K), organic cation transporter 1 (OCT1), and organic cation transporter 2 (OCT2). See Section 4.2.8.1.1 for clinical evaluation.

4.2.8. Summary of Clinical Data

4.2.8.1. Trilaciclib

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

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

- Study G1T28-02 examined once-daily IV administration of either trilaciclib or placebo on Days 1 to 3 of each 21-day E/P chemotherapy cycle in patients with treatment naïve extensive-stage SCLC.
- Study G1T28-03 examined once-daily IV administration of trilaciclib or placebo on Days 1 to 5 of each 21-day topotecan chemotherapy cycle in patients with previously treated extensive-stage SCLC.
- Study G1T28-05 examined once-daily IV administration of trilaciclib or placebo on Days 1 to 3 for a maximum of four 21-day cycles of E/P and atezolizumab, followed by monotherapy atezolizumab, in patients with treatment naïve extensive-stage SCLC.
- Study G1T28-04 examined once-daily IV administration of trilaciclib prior to gemcitabine and carboplatin in patients with metastatic TNBC who had received 0 to 2 lines of previous therapy in the metastatic setting. Patients received 1) 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 recommended phase 2 dose (RP2D) 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, 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 myelopreservation benefits come with an overall improved safety profile compared with available therapy, as evidenced by reduced high grade treatment-emergent AEs across all SCLC studies, and no detriment to anti-tumor efficacy results.

Table 2: Integrated Analysis for Myelopreservation 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; ITT=intent to treat; SN=severe (Grade 4) neutropenia which is defined as ANC < 500/mm3; RBC=red blood cells, SCLC=small cell lung cancer; SD=standard deviation.
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.

Results from the TNBC Study G1T28-04 demonstrated that although the addition of trilaciclib 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, antitumor efficacy results demonstrated- a clinically meaningful improvement in PFS and OS (Figure 2; Table 3). This meaningful antitumor efficacy was observed in both trilaciclib- groups compared with the control group and was also consistent across subgroups, including predictors of immune response. Approximately 57.6% of the available tumor samples in G1T28-04 were considered PD-L1 positive (Ventana SP142 assay), and though larger in the PD-L1 positive population, the benefit of adding trilaciclib extended to both PD-L1 positive and negative cohorts (Table 4).

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

Category	Group 1 GC (Day 1+8) (N=34)	Group 2 GC + Trilaciclib (Day 1+8) (N=33)	Group 3 GC + Trilaciclib (Day 1/2+8/9) (N=35)	Groups 2+3 (N=68)
Overall survival (months) (95% CI)[a, d]				
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)	NE (32.7, NR)
Comparison (treatment group versus Group 1)				
Adjusted HR (SE)[b]	NA	0.31 (0.111)	0.40 (0.125)	0.37 (0.101)
95% CI[b]	NA	0.15, 0.63	0.22, 0.74	0.21, 0.63
2-sided p-value[c]	NA	0.0016	0.0004	<0.0001
Progression-free survival (months) (95% CI)[a, d]				
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)[b]	NA	0.62 (0.209)	0.63 (0.212)	0.62 (0.180)
95% CI[b]	NA	0.32-1.20	0.32, 1.22	0.36, 1.10
2-sided p-value[c]	NA	0.2099	0.1816	0.1291

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

[a] Calculated using the Kaplan-Meier method

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

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

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

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)
p-value	-	0.492	0.075	0.149	-	0.376	0.488	0.943
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)
p-value	-	0.037	0.01	0.004	-	0.077	0.198	0.093
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)

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 and p-values are comparisons between Group 2 and Group 1, Group 3 and Group 1, and between combined Groups 2 and 3 and Group 1.

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

As mentioned in Section 4.2.7, there is a hypothetical risk that administration of trilaciclib prior to chemotherapy could decrease chemotherapy efficacy by pausing CDK4/6-dependent tumor cells in the G_1 phase of the cell cycle in the presence of chemotherapy. 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 the trilaciclib IB).

4.2.8.1.1. Pharmacokinetics

A clinical DDI study using the index CYP3A substrate midazolam indicated that trilaciclib had no impact on CYP3A activity. 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.

Clinical data from the evaluation of trilaciclib administered prior to topotecan (Study G1T28-03) suggests that drugs that are substrates of MATE1 and MATE2 do not pose a clinically relevant

risk of DDIs when administered concomitantly with trilaciclib. In an additional clinical DDI assessment, trilaciclib increased metformin (MATE1, MATE-2K and OCT2 substrate) exposure by 65%, in healthy subjects, compared with administration of metformin alone.

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 with trilaciclib.

Docetaxel has not been reported to be a substrate for MATE1 or MATE2 (Nieuweboer, 2015), and is not believed to be a substrate for OCT2. As such, a clinically significant alteration of docetaxel PK due to trilaciclib inhibition of OCT2, MATE1, or MATE2-K is not expected.

Study G1T28-11 was a single ascending dose study, with both placebo and positive control groups, with the objective to evaluate potential effects of trilaciclib on ECG parameters, including concentration-QTc (C-QTc) analysis. Trilaciclib transiently increased heart rate by approximately 10 beats per minute. At the clinical dose of 240 mg/m^2, trilaciclib did not have a clinically relevant effect on QTc (i.e., >10 msec).

4.2.8.2. Trilaciclib Risks

Reproductive/embryo-fetal effects are an important potential risk of trilaciclib. Both nonclinical toxicology studies with trilaciclib, and clinical studies with other compounds with a similar MOA, report effects on either the reproductive system or embryo/fetus. Since this clinical study will focus on trilaciclib administered prior to cytotoxic chemotherapy (which carries its own risk of reproductive/embryo-fetal toxicity), the risks specific to trilaciclib are consistent with those experienced with chemotherapy. 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.

Adverse events of special interest (AESIs) identified for trilaciclib are described below. Rates reported below reflect those observed in the integrated safety summary from the four Phase 2 oncology studies conducted with trilaciclib to date (G1T28-02 [database lock: 05 May 2019], G1T28-03 [data cutoff: 31 May 2019], G1T28-05 [data cutoff: 28 June 2019], and G1T28-04 [data cutoff: 28 June 2019]). 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 and Section 10.

Trilaciclib AESIs:

1. **Injection Site Reaction/Phlebitis/Thrombophlebitis:** Infusion of trilaciclib may result in local irritation manifesting as erythema, pain, and swelling; and in a subset of patients, the irritation may cause phlebitis/thrombophlebitis. Injection site reactions have been observed in approximately 15 to 20% of patients receiving trilaciclib and the events have

been Grade 1 or 2. Phlebitis/thrombophlebitis has been noted in approximately 5 to 10% of patients receiving trilaciclib and the events were primarily Grade 1 or 2. Supportive care interventions such as slowing the infusion rate, flushing the infusion line with a minimum of 20 mL normal saline or 5% dextrose (D5W), rotating IV catheter sites, and removing the IV (when given peripherally) following each trilaciclib infusion can decrease the frequency and severity of these events. In addition, if symptoms are observed with normal saline as diluent/flush, use of D5W as an alternative may decrease the symptoms. Central access may also be considered.

2. **Acute Drug Hypersensitivity Reaction:** Trilaciclib administration may cause acute drug hypersensitivity reaction characterized by symptoms like angioedema, pruritis, and urticaria. These events have been reported in approximately 6% of patients receiving trilaciclib compared with approximately 3% in patients receiving placebo and were classified as Grade 1 and 2. Only one case of Grade 2 anaphylaxis was observed, which occurred 4 days after the preceding dose of trilaciclib, resolved on the same day, was not serious, and did not result in discontinuation of treatment.

3. **Pneumonitis/Interstitial Lung Disease**: A rare (1 to 3%) but serious class effect (<1% fatal) that is associated with the use of oral CDK4/6 inhibitors. Symptoms include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, or other causes have been excluded. The only case of pneumonitis reported in patients who received trilaciclib was observed in a patient in whom trilaciclib had been discontinued for two months and who had been receiving atezolizumab (known to cause pneumonitis) as monotherapy. The pneumonitis event was Grade 3 and considered by the Investigator to be related to atezolizumab.

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. Studies evaluating the PK of trilaciclib in patients with hepatic impairment are ongoing.

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.

4.2.8.3. Docetaxel

Docetaxel is commonly used in the treatment of metastatic NSCLC (NCCN, 2020) and is approved by the US FDA and the European Medicines Agency for this indication (Taxotere®, 2020; Taxotere, 2005). Per Warnings and Precautions in the prescribing information for docetaxel, the following are important risks related to docetaxel use:

- Acute myeloid leukemia, myelodysplasia or other second primary malignancies
- Cutaneous reactions including erythema, edema and desquamation
- Neurologic reactions including paresthesia, dysesthesia, and pain
- Cystoid macular edema
- Asthenia
- Fetal harm
- Alcohol content (in a dose of Taxotere injection)
- Tumor lysis syndrome
- Neutropenia
- Serious gastrointestinal complications (ex. enterocolitis)
- Hypersensitivity reactions
- Fluid retention
- Respiratory disorders (ex. acute respiratory distress syndrome, interstitial lung disease, pulmonary fibrosis, respiratory failure)
- Severe adverse reactions in patients with liver impairment

4.3. Benefit/Risk Assessment

Trilaciclib (CDK4/6 inhibitor) is being evaluated for anti-tumor efficacy, specifically OS, following disease progression on both immunotherapy and platinum-based chemotherapy, a clinical setting where treatment options are limited and outcomes are suboptimal. In addition to facilitating host immune function, trilaciclib can also provide benefit by making chemotherapy safer and allowing patients to receive the standard of care doses and schedule. These effects have been shown in other trilaciclib clinical trials to improve the patient experience and are provided in the context of minimal toxicity (low grade injection site reactions/phlebitis/thrombophlebitis).

As stated in Section 4.2.8, the dose of 240 mg/m^2 trilaciclib established in the SCLC and TNBC studies (G1T28-04) will be administered prior to a commonly used chemotherapy regimen of docetaxel. The clinically meaningful anti-tumor efficacy results observed in G1T28-04 were noted across multiple endpoints, with OS, PFS, and ORR endpoints all showing numerical improvement with the addition of trilaciclib to GC compared with GC alone.

Studies to date with trilaciclib have demonstrated a manageable safety profile (see Section 4.2.8). Trilaciclib is not expected to have significant overlapping toxicity with docetaxel. In fact,

trilaciclib is expected to have a favorable impact on specific docetaxel complications such as myelosuppression and potentially on gastrointestinal (GI) related side effects.

As described in Section 4.2.9.1 and 4.2.8.1, there is a hypothetical risk that administration of trilaciclib prior to chemotherapy could decrease chemotherapy efficacy by pausing CDK4/6-dependent tumor cells in G1 in the presence of chemotherapy. However, at this time there is no nonclinical (Section 4.2.7) or clinical (Section 4.2.8) evidence to support this theoretical risk. In addition, since sensitivity to CDK4/6 inhibitors is a surrogate marker for CDK4/6 dependence, and the oral, chronically-dosed CDK4/6 inhibitors have shown minimal anti-tumor activity in solid tumors other than ER+ breast cancer (Baghdadi, 2019; Goldman, 2014; Goldman, 2018; Gopalan, 2014; Infante, 2016; Karasic, 2018; Rose, 2018), these results suggest that the majority of solid tumor cancers are not CDK4/6 dependent and not susceptible to this hypothetical risk.

Given the potential benefit to patients with previously treated metastatic NSCLC from the addition of trilaciclib to docetaxel and the limited potential for significant trilaciclib-related toxicity, the benefit/risk assessment is positive for this combination.

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

5. OBJECTIVES AND ENDPOINTS

The primary, secondary, safety, and [redacted] objectives of this study and their associated endpoints, for patients with metastatic NSCLC receiving docetaxel in the 2nd or 3rd line, are presented in Table 5.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To assess the effect of trilaciclib on OS compared with placebo	• OS in the ITT population defined as time from randomization 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 Objectives: Other Anti-Tumor Efficacy	
• To assess the effect of trilaciclib on PFS compared with placebo	• PFS in ITT population defined as time from randomization to 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.
• To assess the effect of trilaciclib on other anti-tumor endpoints compared with placebo	• ORR defined as percentage of patients with confirmed CR and PR per RECIST v1.1 • DOR defined as duration of objective response
Secondary Objective: to evaluate the myelopreservation effect of trilaciclib compared with placebo	
• To assess the effects of trilaciclib on the neutrophil lineage compared with placebo	• Duration of severe (Grade 4) neutropenia in Cycle 1 • Occurrence of severe (Grade 4) neutropenia • Occurrence of febrile neutropenia AEs • Occurrence of G-CSF administration
• To assess the effects of trilaciclib on the RBC lineage compared with placebo	• Occurrence of Grade 3 or 4 decreased hemoglobin laboratory values • RBC transfusions on or after Week 5 (occurrence and number of transfusions) • Occurrence of ESA administration
• To assess the effects of trilaciclib on the platelet lineage compared with placebo	• Occurrence of Grade 3 or 4 decreased platelet count laboratory values • Platelet transfusions (occurrence and number of transfusions)

Objectives	Endpoints
• To assess the effects of trilaciclib on chemotherapy dosing compared with placebo	• All-cause dose reductions (occurrence and number of reductions) • All-cause cycle delays (occurrence and number of delays)
• To assess the effects of trilaciclib on hospitalizations due to chemotherapy-induced myelosuppression compared with placebo	• Occurrence and number of hospitalizations due to chemotherapy-induced myelosuppression
Secondary Objective: to evaluate the safety of trilaciclib compared with placebo	
• To assess the safety and tolerability of trilaciclib compared with placebo	• Occurrence and severity of AEs by NCI-CTCAE v5 • Study treatment discontinuation due to AEs • Changes in laboratory parameters (hematology, chemistry), vital signs and ECG parameters • Grade 3 or 4 abnormalities in laboratory parameters • Trilaciclib AESIs • Chemotherapy infusion interruptions • Relative dose intensity for docetaxel
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
• [redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

AE=adverse event; AESI=adverse event of special interest; BOR=best overall response; CDK=cyclin-dependent kinase; CIM=chemotherapy-induced myelosuppression; DOR=duration of response; ECG=electrocardiogram; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Module; EORTC IL118= European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Module with supplemental weight loss item; EQ-5D-5L=5-level EQ-5D; ESA=erythropoiesis stimulating agent; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy – Fatigue; G-CSF=granulocyte colony-stimulating factor; IV=intravenous; NCI=National Cancer Institute; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic(s); PR=partial response; RBC=red blood cell; RECIST=Response Evaluation Criteria in Solid Tumors

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, global, multicenter, Phase 2 trial evaluating the effect of trilaciclib compared with placebo on OS in patients with metastatic NSCLC receiving docetaxel in the 2nd or 3rd line setting. Patients must have documented disease progression during or after 1 or 2 lines of systemic therapy for recurrent or metastatic NSCLC. Prior treatment must have included, either in the same line or as separate lines of therapy: 1) a maximum of 1 line of platinum-containing chemotherapy in the recurrent/metastatic setting and 2) a maximum of 1 line of a locally approved/authorized PD-1/PD-L1 monoclonal antibody (mAb) containing regimen in the recurrent/metastatic setting.

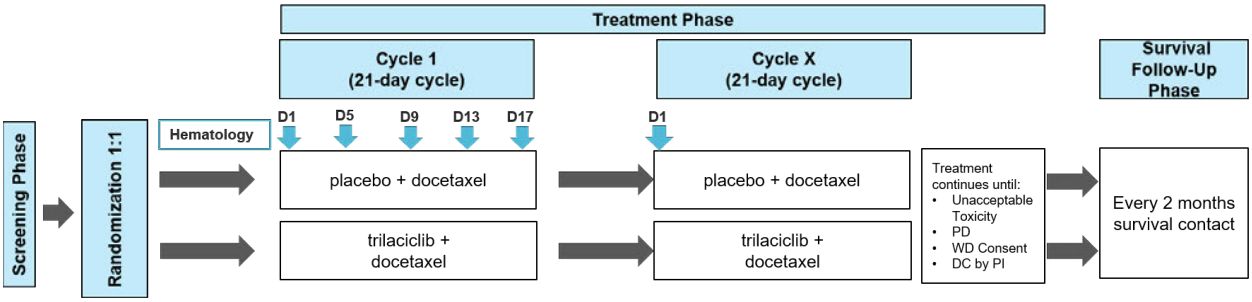
Approximately 146 patients will be randomly assigned (1:1) to receive trilaciclib or placebo by IV prior to docetaxel on Day 1 of each 21-day cycle. There will be 2 stratification factors for randomization: Country, and ECOG performance status (0-1 versus 2). Within each country, patient randomization will be stratified by ECOG performance status (0-1 versus 2).

Study drugs administered are as follows:

- Trilaciclib (240 mg/m^2) or placebo – administered as a 30-minute IV infusion no more than 4 hours prior to chemotherapy on each day chemotherapy is administered (Section 9.1.1).
- Docetaxel 75 mg/m^2 –IV, Day 1

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase (Figure 4). The Treatment Phase begins on the day of randomization for the first patient and completes at the Post-Treatment Visit for the last patient. The first Survival Follow-up assessment should occur approximately 2 months after the last dose of study drug.

Figure 4: Study Design



D=day; PD=progressive disease, WD=withdraw, DC=discontinue

Criteria which patients must meet in order to receive study drug on Day 1 are provided in Section 9.2. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons. Study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or clinical progression as determined by the Investigator, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurs first.

A post-treatment visit will occur approximately 30 days (±7 days) following the last dose of study drug. Upon discontinuation of study treatment, patients will be followed for survival, i.e., patients or their caregivers will be contacted approximately every 2 months until the end of the study (or death) to record their status (alive or dead) as well as details of any subsequent systemic anti-cancer therapy initiated. These survival follow-ups may be done via telephone, email, or clinic visit.

The duration of total follow-up relative to the first patient being randomized is approximately 30 months to collect the target number of deaths per sample size calculation. If assumptions vary in the study conduct, the study duration will be event-driven. That is, the study will continue until the targeted number of deaths is observed. There is an interim analysis for OS. If the interim results demonstrate a statistically significant effect of trilaciclib over placebo for OS based on pre-specified criterion, the study will be stopped early due to success. Otherwise, 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 response rates by RECIST, in addition to OS and PFS, 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 overall survival, 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 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. Myelopreservation Efficacy

Patients experiencing CIM often face severe clinical consequences (e.g., FN, bleeding, fatigue) leading to the need for hospitalizations, hematopoietic growth factor support, transfusions (RBCs and/or platelets) and even death (Caggiano, 2005; Gustinetti, 2016; Bodey, 1966; Li, 2016). Moreover, CIM commonly leads to dose reductions and delays, which limit therapeutic dose intensity and can compromise the anti-tumor efficacy benefits of chemotherapy. In 3 randomized, double-blind, placebo-controlled SCLC trials, the myelopreservation endpoints proposed in this clinical study were utilized to evaluate the efficacy of trilaciclib in reducing CIM. These endpoints proved to be robust measures of trilaciclib's myelopreservation efficacy and clinically meaningful improvements in multiple endpoints were observed across the 3 studies. This study will further investigate the impact of trilaciclib on CIM when used in combination with docetaxel.

6.2.3. Patient-Reported Outcomes

Throughout the trilaciclib clinical development program, patient-reported outcome (PRO) instruments have been evaluated in all randomized clinical trial settings. [redacted]

[redacted] In these studies, trilaciclib generally maintained or reduced fatigue levels across cycles and prevented clinically meaningful increases in fatigue, which are commonly associated with myelosuppression. In G1T28-04 with TNBC patients, patients in the trilaciclib groups were less likely to have a deterioration in their symptoms, and in some cases had improvement in their symptoms, through the first 6 cycles of therapy (last time point evaluated). Trilaciclib delayed deterioration of patient functioning and symptoms measures over time compared with GC alone; suggesting that patients on trilaciclib (compared with GC alone) had a better experience receiving chemotherapy. This study will further investigate the patient experience and potential benefit to NSCLC patients receiving trilaciclib.

6.2.4. Safety

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

6.3. Rationale for Dose and Schedule of Study Treatment

6.3.1. Trilaciclib

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

In addition, at the RP2D, trilaciclib has a limited toxicity profile and minimal overlapping toxicities are expected with docetaxel (Section 4.2.9). The primary AEs anticipated with trilaciclib are low grade injection site reactions including phlebitis/thrombophlebitis. These infusion reactions have generally been mild and occur in association with drug delivery through peripheral access. Central access is likely to reduce/eliminate these issues. The remainder of the trilaciclib AESIs to date have been uncommon and for most, the percentage of patients experiencing these AESIs is not clearly increased in patients receiving trilaciclib compared to placebo. Based on these results a dose-finding study is not needed.

In order to preserve hematopoietic stem and progenitor cells (HSPCs) as well as immune system function during chemotherapy, trilaciclib is always administered prior to systemic chemotherapy (docetaxel), on each day of chemotherapy administration. Trilaciclib will not be administered as monotherapy (i.e., on days that chemotherapy will be delayed).

6.3.2. Docetaxel

The dose and schedule of docetaxel is described in Section 9.1.1.2. This is consistent with standard of care as established in clinical trials (Shepherd, 2000; Garon, 2014), and the approved labeling for this product (NCCN, 2020; Taxotere, 2020; Taxotere, 2005).

6.4. Rationale for Supportive Care Interventions

Per NCCN guidelines docetaxel, as utilized in NSCLC, is considered an intermediate risk regimen with a risk of FN between 10 and 20%. At this level of risk, guidelines do not require routine prophylactic granulocyte colony-stimulating factor (G-CSF) in Cycle 1 (NCCN, 2020b). Therefore, in order to facilitate an unbiased evaluation of trilaciclib effects on the hematologic and pharmacodynamic endpoints, primary prophylactic G-CSF will be prohibited in Cycle 1; however therapeutic G-CSF (administered in response to a neutropenic event) in Cycle 1 and secondary prophylactic G-CSF beginning in Cycle 2 and for all subsequent cycles (i.e., after a precipitating event in a prior cycle of therapy) will be allowed per growth factor/neutropenia management guidelines in Section 9.4 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.

6.5. Rationale for Patient Population

Though immunotherapy has markedly improved the treatment of metastatic NSCLC, options following disease progression remain limited. An alternative therapy that extends the duration of OS without significant additive toxicity, while concurrently decreasing myelosuppression and improving quality of life, would be a welcome addition in this heavily pretreated and often clinically fragile patient population. Therefore, further evaluation of trilaciclib in this area of high unmet medical need is warranted.

6.6. Rationale for Stratification Factors

As outlined in Section 6.1, randomization will be stratified by country and ECOG performance status. Within each country, patient randomization will be stratified by ECOG performance status (0-1 versus 2). These factors were chosen because they are predicted to have an impact on the primary endpoint of overall survival, and in some cases the secondary myelopreservation endpoints, such that if there is an imbalance in these factors, interpretation of the results of the study could be compromised.

Country was chosen as a stratification factor to account for the geographic differences in patient populations, treatment practice patterns and access to supportive care and subsequent anti-cancer therapy; all of which could influence the primary and secondary endpoint outcomes.

Performance status is an established indicator of survival and treatment tolerance. Those with ECOG performance status of 2 typically have shorter survival times and greater toxicity with subsequent therapeutic interventions (Sweeney, 2001; Jang, 2014). However, this group in particular may derive benefit from the myelopreservation and limited toxicity seen with

trilaciclib and has few well-tolerated alternative options. As such, these patients will be eligible but stratified by ECOG performance status (0-1 versus 2) in order to minimize any impact on survival outcomes.

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 of age at the time of signing the informed consent.
2. Histologically or cytologically confirmed metastatic NSCLC (squamous or nonsquamous) with no known actionable driver mutations (ex. EGFR, ROS1, ALK).
    - Patients must have had documented disease progression during or after 1 or 2 lines of systemic treatment for recurrent or metastatic disease.
    - Two components of treatment must have been received in the same line or as separate lines of therapy: (i) a maximum of 1 line of platinum-containing chemotherapy regimen for recurrent/metastatic disease, and (ii) a maximum of 1 line of a locally approved/authorized PD-1/PD-L1 mAb containing regimen for recurrent/metastatic disease.
    - Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate line of therapy. Maintenance therapy is defined as therapy given within 42 days after the last dose of platinum-based chemotherapy in patients with ongoing clinical benefit (complete response [CR], partial response [PR] or stable disease [SD]).
3. Measurable or non-measurable disease per RECIST v1.1
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2
5. A formalin-fixed paraffin-embedded (FFPE) tumor specimen (from archival or fresh biopsy) with an associated pathology report documenting NSCLC must be available to send to the Sponsor, within the specified timeframe, for planned retrospective biomarker analyses (see Section 11.6.1).
6. Adequate organ function defined by the following laboratory values:
    a) Hemoglobin ≥9.0 g/dL in the absence of RBC transfusion or ESA administration within 14 days prior to first dose of trilaciclib/placebo
    b) Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
    c) Platelet count ≥100 × 10^9/L
    d) Total bilirubin ≤ upper limit of normal (ULN)
    e) AST/ALT <1.5 × ULN if alkaline phosphatase >2.5 × ULN
    f) If alkaline phosphatase <2.5 × ULN then AST, ALT <2.5 x ULN in the absence of liver metastasis or <5 × ULN in the presence of liver metastasis

g) Estimated glomerular filtration rate ≥30 mL/minute/1.73m^2

7. Resolution of nonhematologic toxicities per National Cancer Institute Common Terminology Criteria Version 5.0 (NCI-CTCAE) from prior therapy or surgical procedures to ≤ Grade 1 or baseline (except alopecia).
8. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Please see Section 17.3 for detailed instructions on methods of contraception requirements.
9. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

7.2. Exclusion Criteria

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

1. Prior therapy with docetaxel.
2. Any contraindication to the administration of docetaxel at the discretion of the investigator.
3. Mixed NSCLC/SCLC, or lung tumors whose predominant histology is sarcomatoid, or neuroendocrine.
4. Any chemotherapy, immunotherapy, biologic, investigational, or hormonal therapy for cancer treatment (except for adjuvant hormonal therapy for breast cancer or prostate cancer defined as M0 disease or prostate-specific antigen (PSA) persistence/recurrence without metastatic disease) within 3 weeks prior to the first dose of trilaciclib/placebo.
5. Any radiotherapy within 2 weeks prior to the first dose of trilaciclib/placebo.
6. Presence of central nervous system (CNS) metastases requiring immediate treatment with radiation therapy or steroids (i.e., patient must be off steroids administered for brain metastases for at least 14 days prior to the first dose of trilaciclib/placebo).
7. Presence of leptomeningeal disease.
8. Significant third-space fluid retention (ex. ascites or pleural effusion) not amenable to required repeat drainage.
9. QT corrected using Fridericia's formula (QTcF) interval >480 msec at screening (confirmed on repeat). For patients with ventricular pacemakers, QTcF >500 msec.
10. Symptomatic peripheral neuropathy (≥ Grade 2 NCI-CTCAE v5.0)
11. History of interstitial lung disease (ILD)
12. Clinically significant (i.e., active) cardiovascular disease at the time of signing the informed consent; for example cerebrovascular accidents (≤ 6 months before the first dose of trilaciclib/placebo), myocardial infarction (≤ 6 months before the first dose of trilaciclib/placebo), unstable angina, serious cardiac arrythmia requiring medication,

or uncontrolled symptomatic congestive heart failure [Class II or higher as defined by the New York Heart Association [NYHA] functional classification system])

13. Known serious active infection including but not limited to human immunodeficiency virus (HIV) (e.g., viral load indicative of HIV, HIV 1/2 antibodies), Hepatitis B (e.g., HBsAg reactive or HBV DNA detected), Hepatitis C (e.g., HCV RNA [quantitative] is detected) or tuberculosis
14. Prior allogeneic or autologous hematopoietic stem cell or bone marrow transplantation
15. Receipt of any low-dose systemic chemotherapeutic agent (e.g., low-dose methotrexate for rheumatoid arthritis) administered for a nononcologic purpose within 3 weeks prior to the first dose of trilaciclib/placebo.
16. Receipt of any live attenuated vaccines within 4 weeks prior to first dose of study treatment or anticipation that such a vaccine will be required during the study treatment period.
17. Known hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80 or any excipients of trilaciclib
18. Pregnant or lactating women
19. Legal incapacity or limited legal capacity
20. 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
21. Concurrent participation in any other interventional clinical trial.

8. SCHEDULE OF ASSESSMENTS

The procedures and assessments to be performed during the study are outlined in Table 6. The timing and number of samples collected for biomarker testing may be altered based on emerging data without requiring an amendment if the blood volume per day or overall does not increase and the patient is not required to have additional clinic visits or prolongation of a clinic visit, i.e., the risk-benefit profile for the patient does not worsen.

When there are multiple procedures at the same or overlapping time points, order of events should be: patient reported outcome measures, ECGs, vitals, blood draw. 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	Rand	21 Day Treatment [Cycles]						Post-Treatment Visit	Survival Follow-Up	Details Provided in Section
			Cycle 1					Cycle 2 and beyond			
Day	**-28 to -1**	**-3 to -1**	**1**	**5 (±1 day)**	**9 (±1 day)**	**13 (±1 day)**	**17 (±1 day)**	**1[a]**	**30 ±7d post-last dose**	**Every 2 months**	
Informed Consent	X										Section 13.3
Demographics	X										Section 11.1.2
Medical History and NSCLC History	X										Section 11.1.3
Eligibility Evaluation and Randomization	X	X									Section 11.1.1, Section 7.1, and Section 7.2
Archived Tumor Sample	X										Section 11.6.1
ECOG Performance Status	X		X					X	X		Section 11.3.3
Complete physical exam, including height and weight	X										Section 11.3.2
Brief physical exam, including weight			X					X	X		Section 11.3.2
Vital Signs	X		X					X	X		Section 11.3.1
12-lead Electrocardiogram	X		X					X [C2 only]			Section 11.3.4

Assessment	Screening	Rand	21 Day Treatment [Cycles]						Post-Treatment Visit	Survival Follow-Up	Details Provided in Section
			Cycle 1					Cycle 2 and beyond			
Day	**-28 to -1**	**-3 to -1**	**1**	**5 (±1 day)**	**9 (±1 day)**	**13 (±1 day)**	**17 (±1 day)**	**1[a]**	**30 ±7d post-last dose**	**Every 2 months**	
Clinical Chemistry	X		X					X	X		Section 11.3.5
Hematology	X		X	X	X	X	X	X	X		Section 11.3.5
Pregnancy Test (WOCBP)		X	X					X	X		Section 11.3.5
Tumor Assessment by RECIST v1.1	X		X (every 6 weeks from C1D1)							X	Section 11.2.1
Trilaciclib or Placebo			X					X			Section 9.1.1.1.1
Docetaxel			X					X			Section 9.1.1.2
EORTC QLQ-C30, EORTC QLQ-LC13 with supplemental weight loss item (EORTC IL118), FACIT-Fatigue, PGIS, and EQ-5D-5L			X			X		X	X		Section 11.4
PGIC						X		X	X		Section 11.4
Blood Sample for PK			X								Section 11.5

Assessment	Screening	Rand	21 Day Treatment [Cycles]						Post-Treatment Visit	Survival Follow-Up	Details Provided in Section
			Cycle 1					Cycle 2 and beyond			
Day	**-28 to -1**	**-3 to -1**	**1**	**5 (±1 day)**	**9 (±1 day)**	**13 (±1 day)**	**17 (±1 day)**	**1[a]**	**30 ±7d post-last dose**	**Every 2 months**	
Blood Sample for Immunologic and Hematologic Markers			X		X			X [C2, C3, C5 only]			Section 11.7
Survival Contact and Subsequent Anti-cancer Therapies										X	Section 11.10
AEs			X								Section 11.3.6
Concomitant Medications	X	X	X								Section 11.1.3

AE=adverse event; β-hCG=beta human chorionic gonadotropin; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Module; EORTC IL118=European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Module with supplemental weight loss item; EQ-5D-5L=5-level EQ-5D; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy – Fatigue; NSCLC=non-small cell lung cancer; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; Rand=randomization; RECIST=Response Evaluation Criteria in Solid Tumors; WOCBP=women of childbearing potential.

[a] There should be no more than 5 weeks (for toxicity and/or administrative reasons) between doses of chemotherapy; however dosing delays >5 weeks may be permitted on a case by-case basis with the documented approval of the Investigator and Medical Monitor.

9. STUDY TREATMENT

9.1. Study Drugs Administered

Study drugs are defined as any investigational agent(s), marketed product(s), or placebo 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

	Study Drugs		
Product Name:	Trilaciclib	Placebo	Docetaxel
Type	Investigational product	Placebo	Chemotherapy
Dosage Formulation:	Single-use, sterile powder to be reconstituted with 250 mL of dextrose 5% in water (D5W) or normal saline (sodium chloride solution 0.9%) per the Pharmacy Manual	250 mL of dextrose 5% in water (D5W) or normal saline (sodium chloride solution 0.9%)	Description of the formulation is provided in the current prescribing information (Taxotere, 2020; Taxotere, 2005)
Unit Dose Strength(s)	300 mg/20 mL	N/A	See current prescribing information
Dosage Level(s)	240 mg/m^2	N/A – administered on Day 1 to match trilaciclib	75 mg/m^2
Route of Administration	IV	IV	IV
Infusion Time	30 minutes	30 minutes	1 hour or per Institutional Standards

IV=intravenous; N/A=not applicable.

9.1.1. Dose, Dosing Regimen, and Route

9.1.1.1. Trilaciclib/Placebo

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. BSA should be calculated as per institutional practice. Actual body weight (not "adjusted" 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.

The placebo, either 250 mL of dextrose 5% in water (D5W) or sodium chloride solution 0.9%, will be administered by IV infusion over approximately 30 minutes by peripheral or central access.

9.1.1.1.1. Administration of Trilaciclib/Placebo

- Administer diluted trilaciclib solution or placebo as a 30-minute IV infusion completed within 4 hours prior to the start chemotherapy. Do not administer trilaciclib/placebo as a bolus.
- Trilaciclib/placebo is always administered first. Results from hematology labs should be reviewed prior to administration of trilaciclib/placebo. If administration of docetaxel therapy is delayed or discontinued, trilaciclib/placebo will also be delayed or discontinued.
- Diluted trilaciclib/placebo solution must be administered with an infusion set, including an in-line filter (0.2 or 0.22 micron). Compatible in-line filters include polyethylene sulfone, polyvinylidene fluoride, and cellulose acetate.
- Do not administer diluted trilaciclib/placebo solution with a polytetrafluorethylene (PTFE) in-line filter. PTFE in-line filters are not compatible with diluted trilaciclib/placebo 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.

Upon completion of infusion of diluted trilaciclib/placebo solution, the infusion line/cannula must be flushed with at least 20 mL sterile D5W or 0.9% normal saline.

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

9.1.1.2. Docetaxel

Docetaxel will be administered IV in accordance with the prescribing information/summary of product characteristics (Taxotere, 2020; Taxotere, 2005) and according to the study site's standard practice. Protocol-specified doses of docetaxel will be administered IV in accordance with institutional guidelines and the recommended instructions below. Deviation from the recommendations provided in this protocol in order to follow institutional guidelines must receive prior approval from the Medical Monitor or Sponsor.

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.

Trilaciclib/placebo is always administered first, followed by docetaxel. Administer diluted trilaciclib solution or placebo as a 30-minute IV infusion to be completed within 4 hours prior to the start chemotherapy. Docetaxel may be administered immediately following trilaciclib/placebo, but not until the completion of the trilaciclib/placebo infusion. If administration of trilaciclib/placebo is delayed or discontinued, docetaxel will also be delayed or discontinued. Likewise, if docetaxel is delayed or discontinued, trilaciclib/placebo will also be delayed or discontinued.

9.1.2. Preparation, Handling, Storage, and Accountability

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

Further guidance and information are provided in the Pharmacy Manual.

9.1.3. Treatment Compliance

The Investigator or designee will dispense the study drugs, via an unblinded 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 and end of each trilaciclib or placebo and docetaxel infusion; and total drug administered in milligrams. 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 Each Cycle

Patients must meet all the following minimum criteria to receive study treatment on Day 1 for Cycle 1 and each subsequent cycle:

- ANC $\geq 1.5 \times 10^9$/L,
- Platelet count $\geq 100 \times 10^9$/L
- Total bilirubin $\leq$ upper limit of normal (ULN)
- AST/ALT $\leq 1.5 \times$ ULN if alkaline phosphatase $>2.5 \times$ ULN
- Other nonhematologic drug-related toxicities (excluding alopecia) must be $\leq$ Grade 1 or have returned to baseline.

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 described above are met or until they discontinue treatment (e.g., if more than 5 weeks elapse from the last chemotherapy dose). If the Day 1 dose is delayed, any assessments completed as part of the planned Day 1 visit will be captured in the eCRF as unscheduled visits. The PRO questionnaires should be completed on both the planned Day 1 visit and on the actual Day 1 of the cycle (i.e., when criteria are met to proceed with Day 1 treatment).

There should be no more than 5 weeks (for toxicity and/or administrative reasons) between doses of chemotherapy; however dosing delays >5 weeks may be permitted on a case by-case basis with the documented approval of the Investigator and Medical Monitor.

In both the trilaciclib and placebo arms, 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.

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 docetaxel therapy is discontinued, trilaciclib will also be discontinued.

The dose of docetaxel can be reduced when necessary as described below. The recommended dose modification procedures for hematologic toxicities are described in Table 9. 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 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.

Non-hematologic toxicities should be managed as per standard of care for docetaxel. Recommendation for management of trilaciclib/placebo AESIs are provided in Table 10. Recommendations for hepatobiliary toxicity management are in Section 9.3.4. All recommendations are intended as a minimum guideline for toxicity management and are not a replacement for independent medical judgement tailored to specific circumstances with an individual patient. Please also refer to the individual package insert/summary of product characteristics (Taxotere, 2020; Taxotere, 2005) for additional information and recommendations.

9.3.1. Dose reduction

Recommended dose levels for reduction of docetaxel dose are described in Table 8. Chemotherapy dose reductions for hematologic toxicities should be based on values obtained within 24 hours prior to Day 1 of a given cycle. 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.

Table 8: Recommended Chemotherapy Dose Modifications

	Docetaxel
Starting Dose	75 mg/m^2
Dose Level -1	60 mg/m^2
Dose Level -2	50 mg/m^2

No dose modification is permitted for trilaciclib.

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, FN, serious adverse event (SAE) or other consequence, do not require dose modification.

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

9.3.2. Safety Criteria for Adjustment or Stopping Doses

Table 9: Recommended Dose Modification for Drug-Related Hematologic Toxicity

		Action Taken		
Event, CTCAE Grade or Lab Value	**Frequency**	**Trilaciclib**	**Docetaxel**	**Toxicity Management**
ANC <1.5 x 10^9/L (≥Grade 2)	1st occurrence	Hold drug until ANC criteria for dosing reached. No change in dose.	Hold drug until ANC criteria for dosing reached. No change in dose.	Administer prophylactic G-CSF with each subsequent cycle of chemotherapy.
	2nd occurrence	Hold drug until ANC criteria for dosing reached. No change in dose.	Hold drug until ANC criteria for dosing reached. Reduce dose of docetaxel by one dose level and resume dosing.	
	3rd occurrence	Hold drug until ANC criteria for dosing reached. No change in dose.	Hold drug until ANC criteria for dosing reached. Reduce dose of docetaxel by one more dose level and resume dosing.	
	4th occurrence	Permanently discontinue		
Febrile neutropenia (Grade 3 or 4) OR Grade 4 Neutropenia lasting >7 days	1st occurrence	Hold drug until ANC criteria for dosing reached. No change in dose.	Hold drug until ANC criteria for dosing reached. Reduce dose of docetaxel by one dose level and resume dosing.	Administer prophylactic G-CSF with each subsequent cycle of chemotherapy.
	2nd occurrence	Hold drug until ANC criteria for dosing reached. No change in dose.	Hold drug until ANC criteria for dosing reached. Reduce dose of docetaxel by one more dose level and resume dosing.	
	3rd occurrence	Permanently discontinue		
Platelets <100 - 75 x 10^9/L (Grade 1)	Any occurrence	Hold drug until platelet criteria for dosing reached. No change in dose.	Hold drug until platelet criteria for dosing reached. No change in dose.	Monitor for signs and symptoms of bleeding. Consider treatment as clinically indicated

		Action Taken		
Event, CTCAE Grade or Lab Value	**Frequency**	**Trilaciclib**	**Docetaxel**	**Toxicity Management**
Platelets <75 - 50 x10^9/L (Grade 2)	1st Occurrence	Hold drug until platelet criteria for dosing reached. No change in dose.	Hold drug until platelet criteria for dosing reached. No change in dose.	Monitor for signs and symptoms of bleeding. Consider treatment as clinically indicated
	2nd Occurrence	Hold drug until platelet criteria for dosing reached. No change in dose.	Hold drug until platelet criteria for dosing reached. Reduce dose of docetaxel by one dose level and resume dosing.	
	3rd Occurrence	Hold drug until platelet criteria for dosing reached. No change in dose.	Hold drug until platelet criteria for dosing reached. Reduce dose of docetaxel by one dose level and resume dosing.	
	4th Occurrence	Permanently discontinue		
Platelets <50 x 10^9/L (≥Grade 3) OR Symptomatic thrombocytopenia (severe or medically significant bleeding)	1st occurrence	Hold drug until platelet criteria for dosing reached. No change in dose.	Hold drug until platelet criteria for dosing reached. Reduce dose of docetaxel by one dose level and resume dosing.	Monitor for signs and symptoms of bleeding. Consider treatment as clinically indicated
	2nd occurrence	Hold drug until platelet criteria for dosing reached. No change in dose.	Hold drug until platelet criteria for dosing reached. Reduce dose of docetaxel by one more dose level and resume dosing.	
	3rd occurrence	Permanently discontinue		

ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte colony-stimulating factor.

9.3.3. Recommended Actions with Trilaciclib/Placebo for Adverse Events of Special Interest

Suggested actions to be taken with trilaciclib/placebo following AESI are provided in Table 10.

Table 10: Recommended Actions with Trilaciclib/Placebo 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 Activities of Daily Living	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.

AESI	Severity	Recommended Action
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.
	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.
Other toxicities	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Hold trilacicib until recovery to Grade ≤1 or baseline, then consider resuming trilaciclib. If Grade 3 recurs, permanently discontinue trilaciclib.
	Grade 4: Life-threatening consequences; urgent intervention indicated.	Permanently discontinue trilaciclib

AESI=adverse event of special interest; ILD=interstitial lung disease

9.3.4. Hy's Law Management

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

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 (PT)/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 SAE 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 regional guidelines or consensus (e.g., American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO], Chinese Anti-Cancer Association) and package inserts/summary of product characteristics.

If in any cycle (including Cycle 1), a patient experiences severe neutropenia (Grade 4) or FN and is at high risk for infection associated- complications or has prognostic factors that are predictive of poor clinical outcomes (Table 11), therapeutic G-CSF/GM-CSF may be used to treat the severe neutropenia or FN event per regional guidelines and package inserts.

Short-acting G-CSF products (i.e., Neupogen or biosimilars) may be administered starting 24 to 48 hours after chemotherapy 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 (ex. macapegfilgrastim) may be administered 24 to 48 hours after chemotherapy but due to its prolonged half-life should not be repeated within that cycle. Biosimilars must be approved for use by the national regulatory authority (ex. FDA, European Commission, or the China National Medical Products Administration [NMPA]).

Table 11: Patient Risk Factors for Poor Clinical Outcomes Resulting from Febrile Neutropenia or Infection

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

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

9.4.2. Erythropoiesis-Stimulating Agent Usage

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

9.4.3. Transfusions

Red Blood Cells

Based on the NCCN Clinical Practice Guidelines in Oncology for Hematopoietic Growth Factors Version 2.2020 and the AABB Clinical Practice Guidelines, the following RBC transfusion thresholds are recommended (Carson, 2016; Goel, 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 × 10^9/L. Platelets should also be transfused in any patient who is bleeding with a platelet count <50 × 10^9/L (100 × 10^9/L for central nervous system or ocular bleeding) (Kaufman, 2015; Schiffer, 2017).

9.5. Prior/Concomitant Medications and Procedures

All concomitant medications including prescription medications, over-the-counter preparations, growth factors, and blood products from informed consent through 30 days after the last dose of study treatment (Post-Treatment Visit) will be documented, where possible. During the study,

prescription, and commercially available products, including traditional Chinese medications, with known or suspected immunomodulatory properties should be used with caution or avoided entirely.

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 (Section 4.2.8.1.1).

Docetaxel is a CYP3A4 substrate. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Any medication that is contraindicated when using docetaxel is not permitted, and special warnings and precautions for use of docetaxel should be observed.

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, with the exception of adjuvant endocrine therapy for breast cancer or prostate cancer defined as M0 disease or PSA persistence/recurrence without metastatic disease. This includes any low-dose systemic chemotherapeutic agent given for a nononcologic purpose (e.g., low-dose methotrexate for rheumatoid arthritis). 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 (target or nontarget lesion), then “not evaluable” should be reported in electronic data capture (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: Randomization and Blinding

The study will be randomized and double-blind. Patients meeting all inclusion and exclusion criteria will be randomized 1:1 by an Interactive Web Response System (IWRS) according to a randomization schedule generated by an unblinded external statistician. Each patient will be assigned a unique randomization number, which will not be reused. A patient who is randomized and discontinues from the study, even if no study drug was administered, will not be replaced. If

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

There will be 2 stratification factors for randomization: country and ECOG performance status (0-1 versus 2). Within each country, patient randomization will be stratified by ECOG performance status (0-1 versus 2).

Each site will have an unblinded Pharmacist/Designee, who will have access to the treatment assignment. Because the active drug product trilaciclib has a faint yellow color when reconstituted and diluted, additional procedures will be implemented to ensure the blind is maintained for the patient, Investigator, Research Nurse, Study Coordinator, and other blinded site personnel. Details regarding the preparation and administration of trilaciclib/placebo in a manner to maintain the blind will be included in the Pharmacy Manual.

The patients, Investigators, other site staff involved in the clinical care of the patients, and the Sponsor or Designees involved in the conduct of the study will not be aware of the treatment group to which a particular patient has been randomized. If an Investigator determines that a patient's assignment should be unblinded for reasons of safety, this should be discussed with the study Medical Monitor prior to unblinding, unless an urgent and immediate intervention is required that precludes this discussion. If unblinding of the treatment assignment is necessary, the Investigator or Designee will obtain the treatment assignment details from the IWRS. Unblinding of personnel should be limited to the minimum needed for mitigation of safety concern. Following unblinding, patient continuation on study will be determined on a case by case basis. Any unplanned unblinding must be communicated to the Project Manager, Study Statistician, and Sponsor for documentation in the study files and the clinical study report.

If the blinding code is broken, the date and reason for unblinding must be fully documented in source documents and entered on the eCRF. However, every effort should be made by the site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

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 11.10).

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 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 total time between chemotherapy treatments exceeds a total of >5 weeks, unless agreed to by the treating Investigator and Medical Monitor.
- Where permanent discontinuation of all study drugs is indicated in the toxicity management recommendations

At the time of study drug discontinuation, a Post-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 medication, 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 patient has not already

discontinued study intervention, a Post-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 subject 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, the study will continue until the targeted number of deaths is observed. There is an interim analysis for OS planned when approximately 73 patients have died. If the interim results demonstrate a statistically significant effect of trilaciclib over placebo for OS based on pre-specified criterion, the study will be stopped early due to success. Otherwise, the study will continue and be considered complete when the targeted number of deaths have occurred for the final OS analysis (approximately 104 deaths), or upon sponsor termination of the study.

The Sponsor’s designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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, clinical chemistry) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and are performed within 28 days prior to Cycle 1 Day 1.

11.1. Screening Assessments

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

11.1.1. Randomization

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

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

Randomization will be performed via IWRS and can be completed up to 3 days prior to the first dose of trilaciclib or placebo + docetaxel therapy, following confirmation that the patient is eligible for the study. Patients can also be randomized and receive Cycle 1 Day 1 on the same day. When required by institutional procedures, randomization will be allowed up to 7 days prior to dosing without a protocol deviation. Screening procedures must be completed prior to randomization and the screening window remains 28 days.

11.1.2. Demographics

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

11.1.3. Medical History and NSCLC Cancer Disease History

Medical and surgical history, including past and current conditions, will be collected. Concomitant medications taken from informed consent through 30 days after the last dose of study treatment will be recorded. Prior medications (those taken within 14 days of informed consent will also be recorded.

Documentation of NSCLC history, including date of diagnosis and histologic type, as well as prior therapy (ex. surgery, radiation, systemic chemotherapy, immunotherapy) for NSCLC will also be recorded. PD-L1 status will be collected and recorded where available.

11.2. Anti-tumor Efficacy Assessments

11.2.1. Anti-tumor Efficacy Assessment

Tumor assessment will be performed at the timepoints specified in the Schedule of Assessments (Table 6) relative to Cycle 1 Day 1, regardless of drug (cycle) delays.

Baseline imaging should include computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and brain. IV contrast should be used unless contraindicated. Any CT or MRI obtained as standard of care prior to signing the informed consent will not need to be repeated as long as those imaging tests were obtained within 28 days prior to Cycle 1 Day 1.

After baseline tumor assessments (Screening assessment within 28 days prior to Cycle 1 Day 1), evaluation of tumor response per RECIST v1.1 will be performed every 6 weeks following Cycle 1 Day 1 (±7 days) during study drug administration (including imaging of the chest, abdomen, and pelvis [and brain if metastasis present at Screening or if symptoms develop]), with additional scans performed as clinically indicated. Post-baseline tumor assessments should use the same imaging modality as at Screening. IV contrast should be used unless contraindicated. Tumor assessments will continue until disease progression, withdrawal of consent, initiation of subsequent anti-cancer therapy, or the end of study, whichever occurs first.

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, until the occurrence of progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

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 at the next scheduled tumor assessment per RECIST v1.1.

During the course of this study, scans may be collected and sent/uploaded to the Sponsor or Designee for storage. Centralized storage is intended for possible blinded independent central review (BICR) of disease assessments. At the discretion of the Sponsor, BICR of all scans by RECIST v1.1 may be conducted retrospectively. The blinded review will include all patients with available images. However, the raw images for patients enrolled in China cannot be stored outside of China and therefore these images will be stored in the server in China for central imaging review if approved by the related authority. If needed, guidelines for imaging collection and storage will be provided in a separate document. The clinical management of patients will be based solely upon the results of the assessment conducted by the Investigator based on RECIST v1.1 per protocol.

11.2.2. Myelopreservation Assessments

The myelopreservation effects of trilaciclib administered prior to docetaxel compared with placebo administered prior to docetaxel will be evaluated based on the following: kinetics of changes in CBCs (including DSN in Cycle 1 and rate of SN); hematologic toxicities, including FN; RBC and platelet transfusions; hematopoietic growth factor utilization; infections and systemic antibiotic use. All of these variables will be assessed as described in the safety assessments (monitoring of AEs, clinical laboratory assessments, and concomitant medications).

11.3. Safety Assessments

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

11.3.1. Vital Signs

The following will be collected per the Schedule of Assessments (Table 6) 15 minutes (+/- 10 minutes) before and after the trilaciclib/placebo infusion:

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

11.3.2. Physical Examination

Full physical examination at Screening should include general appearance, height in centimeters, body weight in kilograms, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, lymph nodes, extremities, and neurological examinations. Subsequent physical exams should include body systems as determined by provider (e.g., brief physical exam) 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 12) as well as to monitor performance throughout the study (Table 6).

Table 12: 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 out any selfcare. Totally confined to bed or chair
5	Dead

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

11.3.4. Electrocardiogram

Single standard 12-lead ECGs will be performed as outlined in the Schedule of Assessments (Table 6) on Day 1 of Cycles 1 and 2 at the following timepoints: predose (any time prior to trilaciclib/placebo on the day of dosing) and at the end of trilaciclib/placebo infusion (within 30 minutes following the infusion but prior to initiation of docetaxel infusion). 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 5 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. A repeat ECG in triplicate (over approximate 5-minute period) should also be obtained for confirmation. 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.

11.3.5. Clinical Safety Laboratory Assessments

Hematology, clinical chemistry, and serum or urine pregnancy test 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 the Investigator's clinic following approval by the Medical Monitor. A list of clinical laboratory tests to be performed is provided in Section 17.1. Hematology may be obtained up to 24 hours and serum chemistry may be obtained up to 72 hours prior to each time point on Schedule of Assessments but must be reviewed before dosing. Laboratory toxicities will be assessed using the NCI-CTCAE, v5.0.

For women of childbearing potential, pregnancy tests will be performed as follows: serum beta human chorionic gonadotropin (ß-hCG) at Screening (must be performed during window allowing randomization in IWRS and negative results should be available prior to

randomization) and serum or urine ß-hCG prior to the start of each cycle thereafter, as well at the post-treatment visit.

An abnormal laboratory value is not an AE unless it is considered to be clinically significant. Whether a clinically significant laboratory value is also an adverse event will be determined 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 for toxicity, the patient should still complete the clinical laboratory assessments on the scheduled Day 1 (entered as an Unscheduled assessment in 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 (see Section 9.3.2; Table 9).

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 Post-Treatment 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, Inc. 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, Inc. 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, Inc.

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, Inc. PVG or designee by the Investigator (or designee) of a 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, Inc. 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, Inc. 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, Inc. 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, Inc. 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, Inc. 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. Patient-Reported Outcomes

The PRO items below will be self-administered by patients, overseen by a designated study site staff member. PRO questionnaires should be completed on Days 1 and 13 of Cycle 1 and Day 1 of each subsequent cycle and at the Post-Treatment Visit, except for the Patient Global Impression of Change (PGIC) which is not administered on Day 1 of Cycle 1, per the schedule outlined in the Schedule of Assessments (Table 6).

The PRO questionnaires should be completed on both the planned Day 1 visit and on the actual Day 1 of the cycle (i.e., when dosing is delayed and criteria are then met to proceed with Day 1 treatment). PRO questionnaires may be administered up to 1 calendar day prior to each dosing day and are to be completed on the same day a blood sample is collected for hematology assessment. Questionnaires administered on Cycle 1 Day 13 may be obtained ±1 day of scheduled visit. Questionnaires should be completed before treatment administration, and where possible before any laboratory tests or other procedures that are performed that day.

11.4.1. EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 and QLQ-LC13 are validated instruments that will be administered on the days outlined in the Schedule of Assessments (Table 6).

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials (Aaronson, 1993). The core questionnaire, the QLQ-C30, includes 30 items that address symptoms and functional impacts that are applicable across cancer populations. The QLQ-C30 yields 15 domains assessing global health status, symptoms (e.g., fatigue, nausea and vomiting), and function (e.g., physical functioning, emotional functioning). Each domain is scored on a 0-100 scale. The detailed scoring algorithm is included in the scoring manual (Fayers, 2001).

The EORTC QLQ-LC13 is a supplemental module that was designed for use among a wide range of lung cancer patients varying in disease stage and treatment modality (Bergman, 1994). The QLQ-LC13 incorporates one multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. Domains are scored on a 0-100 scale. The open-ended item assessing location of pain and the item asking about the use and effect of pain medications will not be included in the QLQ-LC13 version to be administered in this trial, as it is not used in the scoring of the measure. A supplemental item from the EORTC Item Library addressing weight loss ("Has weight loss been a problem for you?") will be added to the QLQ-LC13. This version of the QLQ-LC13 has been titled the EORTC IL118 by the EORTC. The scoring algorithm is described in the scoring manual (Fayers, 2001).

11.4.2. FACIT-Fatigue

The is FACIT-Fatigue (Yellen, 1997) is a 13-item measure that measures the severity of fatigue (e.g., "I feel fatigued," "I feel tired") and the impact of fatigue on functioning (e.g., "I have trouble starting things because I am tired," "I need to sleep during the day"). Patients rate their experiences over the "past 7 days" using a 0-4 verbal rating scale ("Not at all" to "Very Much"). The FACIT-Fatigue is scored as a sum of all 13 of the item responses; the scale range is from 0-

52. After appropriate reverse scoring of 11 items, lower scores on the FACIT-F indicate greater levels of fatigue.

11.4.3. Patient Global Impression of Change and Patient Global Impression of Severity

The PGIC and Patient Global Impression of Severity (PGIS) items will be self-administered on the days outlined in the Schedule of Assessments (Table 6). The PGIC item will ask the patient to rate the change in their fatigue since taking study drug on a 7-point scale ranging from -3 (very much worse) to 3 (very much better). The PGIS item, will ask the patient to rate the overall severity of their fatigue over the past week on a 5-point scale ranging from 0 (none) to 4 (severe).

11.4.4. 5-Level EQ-5D

The EQ-5D-5Lwill be provided to patients for self-administration on the days outlined in the Schedule of Assessments (Table 6). The 5-level EQ-5D (EQ-5D-5L) is a standardized instrument by which treatment effects can be assessed by measuring health status at different points in time, e.g., before and after treatment, and then investigating the gains (or losses) in reported health status. The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). For the EQ-5D, respondents will rate their health on each of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient will be asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ-VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine". The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

11.5. Pharmacokinetics

Blood samples for PK analysis will be collected as indicated in the Schedule of Assessments (Table 6) from all patients. Three blood samples for PK analysis of trilaciclib will be collected: on Cycle 1 Day 1 at the end of trilaciclib/placebo infusion (sample can be taken up to 15 minutes prior to the end of infusion), at 30 minutes post the end of trilaciclib/placebo infusion (±15 minutes) and at 4-6 hours post the end of the trilaciclib/placebo infusion.

Three samples will also be collected for PK analysis of docetaxel: on Cycle 1 Day 1 at the end of docetaxel infusion (sample can be taken up to 15 minutes prior to end of infusion), 2 hours after end of docetaxel infusion (±30 minutes) and at 4-6 hours post the end of the docetaxel infusion.

The actual date and time of each blood sample collection, the scheduled timepoint of collection, and the time of dose administration prior to the pharmacokinetic sample will be recorded. Details of PK blood sample collection including volume to be collected, timing of samples, processing, storage, and shipping procedures are provided in the Laboratory Manual. Blood samples for PK analysis may be collected from patients at a different location than Investigator's clinic.

11.6. Biomarkers

11.6.1. Rationale for Archival Tumor Collection

Because trilaciclib maintains G1 arrest in CDK4/6 dependent cells, there is a hypothetical risk that trilaciclib could antagonize the anti-tumor efficacy of cytotoxic chemotherapy by maintaining a G1 cell cycle arrest of CDK4/6 dependent tumor cells during chemotherapy. While the currently available nonclinical and clinical data indicate that this risk remains hypothetical and does not influence the overall benefit/risk assessment for combining trilaciclib with chemotherapy, this study will evaluate in a retrospective fashion the relationship between CDK4/6 status and measures of anti-tumor efficacy; the planned statistical analyses are described in Section 12.4.9.

To support these analyses, prior to signing the informed consent, a FFPE archival tumor specimen with an associated pathology report documenting NSCLC (recurrent/metastatic preferred) for each patient must be confirmed to be available to send to a central storage facility for planned retrospective biomarker analyses. Tumor tissue must consist of a fixed paraffin-embedded block (100 microns preferred; 75 microns (minimum) unless otherwise approved by the Medical Monitor. If a block is not available, 20 or more (15 minimum) freshly cut unstained slides are an acceptable alternative. If archival tissue is not available, a fresh biopsy must be obtained. Acceptable samples include core needle biopsies, tumor tissue - excisional or incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. Additional guidance is provided in the Laboratory Manual.

In addition to CDK4/6 status as described below, tumor PD-L1 status (positive or negative) will be determined and anti-tumor efficacy endpoints by PD-L1 status will be evaluated. Any remaining tumor tissue following the described analyses will be banked and may be analyzed for relevant DNA, ribonucleic acid (RNA), or protein biomarkers and their role in cancer, including to better understand immune-related mechanisms.

Note: No tumor tissue will be archived for study centers in China.

11.6.2. Description of CDK4/6 Signature

In order to characterize this hypothetical risk in a tumor type without a clear CDK4/6 response phenotype, archival tumor tissue will be collected from patients' most recent biopsy (NSCLC primary or metastatic site) and subjected to a genetic signature analysis based on published literature in an effort to characterize patient tumors into one of the following three groups (Gong, 2017; Shapiro, 2017):

- CDK4/6 independent
- CDK4/6 dependent
- CDK4/6 indeterminate

The evaluation of the relationship between CDK4/6 status and anti-tumor outcomes may be performed when the final OS analysis is performed, that is, when the predicted death events are observed. The use of mature OS data, in addition to the ORR and PFS data, will allow for a more robust interpretation of the relationship between CDK4/6 status and anti-tumor outcomes without

the complication of trying to draw conclusions with inadequate information (i.e., immature anti-tumor efficacy data).

This timing is considered to be appropriate since all currently available data indicate that if there is a risk, it is not clinically relevant; therefore, waiting until mature OS data does not pose a significant hazard to the enrolled patients, particularly since the percentage of patients at risk for a potential negative outcome (i.e., who have CDK4/6 dependent tumors) is predicted to be <10% (Section 4.2.7).

11.7. Immunologic and Hematologic Markers

Blood samples for biomarker analysis will be collected at the time points indicated in the Schedule of Assessments (Table 6) from all patients.

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

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

To evaluate the impact of trilaciclib administration on chemotherapy-induced changes of the immune and hematopoietic system, immunophenotypic and hematologic changes will be compared (as data warrant) between trilaciclib and placebo on patients receiving docetaxel therapy. To assess these changes, peripheral blood will be collected per the timepoints in the Schedule of Assessments (Table 6). At each time point (Cycle 1 Day 1, Cycle 1 Day 9, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1), collection should occur prior to trilaciclib dosing.

These blood samples will be banked and may be analyzed for relevant DNA, RNA, or protein biomarkers and their role in cancer. Samples may be stored for up to 10 years if patients sign the consent form and allow their samples to be stored for any future research. Note: No blood will be archived for study centers in China.

11.8. Data Monitoring Committee

An unblinded, independent Data Monitoring Committee will monitor accumulating safety and disposition data with the first meeting planned for when approximately 20 patients have enrolled and completed at least 2 cycles of study treatment. The meetings will continue approximately every 4 months while patients are on study treatment depending upon the enrollment rate. Additional reviews may occur based on DMC requests.

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

11.9. Post-Treatment Visit

When a patient permanently discontinues study treatment, the patient should complete a Post-Treatment Visit 30 days (± 7 days) from last dose of study drug as outlined in Table 6.

11.10. Survival Follow-up Phase

Starting from the last dose of study drug, the patient will be followed approximately every 2 months for survival. Survival Follow-up Visits can be via telephone, email, or clinic visits.

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.

Information will be collected until the end of the study (or death) to record their 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 guidance.

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 determined to support the primary objective of the study. That is, to evaluate the effect of trilaciclib compared to placebo on the overall survival of patients with metastatic NSCLC receiving docetaxel in the 2nd/3rd line setting. A total of 104 deaths will be required to achieve 85% power to detect a hazard ratio (HR) of 0.55 in OS at a 2-sided significance level of 0.05. A HR of 0.55 corresponds to a median OS of 16.5 months for the trilaciclib group assuming a median OS of 9.1 months for the placebo group (Garon, 2014). With a 12-month enrollment period and a 30-month study duration (after the first patient is randomized), a total of 146 patients are required for randomization at a 1:1 ratio to trilaciclib or placebo. This sample size has taken into consideration an interim analysis for OS at the information fraction of 0.70 using the O'Brien-Fleming method for α-spending to ensure strong control of Type I error rate at 1-sided 0.025 between the interim and the final analysis for OS. In the sample size calculation, it is also assumed that about 5% of patients are lost-to-follow-up during the 30-month study duration. EAST® v6.5 is used for the power and sample size calculations.

12.2. Analysis Population

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

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

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

The pharmacokinetic (PK) population will include all patients who received at least one dose of study drug and had evaluable PK data.

12.3. Timing of Planned Analysis

12.3.1. First Planned Analysis – Interim Analysis for Overall Survival and Analyses for Progression Free Survival, Tumor Responses and Myelosuppression Endpoints

The first planned analysis will take place primarily to perform the interim analysis for OS. The timing of this analysis will be based on the timing when 73 deaths are observed. Following the

assumptions that are used in the sample size calculation (Section 12.1), this analysis might be conducted approximately 19 months after the first patient is randomized.

Per literature, the expected median PFS for patients receiving docetaxel is 3 months (Garon, 2014). Assuming trilaciclib can achieve a treatment effect of HR of 0.60, it is estimated that at the time of performing the OS interim analysis, 86% of patients would have had radiographic-determined disease progression or died. Therefore, the analysis for PFS will be conducted at the time when the OS interim analysis is conducted since the PFS events are considered mature. It is also anticipated that the treatment effect on tumor response will be mature at this time, thus, ORR and DOR will also be analyzed at this time. In addition, analyses for myelosuppression and PRO endpoints will be performed at this time.

The study database will be locked to perform these planned analyses.

If the interim OS analysis result is positive as determined by the pre-specified statistical criterion, the study will be stopped for success and the OS analysis results are considered final. If the interim OS analysis result does not meet the criterion of success, the study will continue until a total of 104 deaths are observed.

12.3.2. Second Planed Analysis – Final Analysis for Overall Survival and Safety Data Analyses

At the time when 104 deaths are observed, the study database will be locked to perform the final analysis for OS. This will be the closure of the study. Safety data and anti-tumor efficacy evaluation by CDK 4/6 status and [redacted] analyses will be performed at this time. Under the assumptions used in sample size calculation (Section 12.1), this analysis could be performed approximately 30 months after the first patient is randomized.

It is expected that PFS data are mature at the time of performing the OS interim analysis (i.e., the first planned analysis). However, if the percentage of patients with a radiographic determined disease progression or death at the time of the first planned analysis is less than 80%, PFS will be analyzed again at this time and the results from this analysis will be considered as primary to interpret trilaciclib's effect on PFS in this study.

At this time, other SAP specified analyses that are not mentioned in Section 12.3.1 will all be conducted.

12.4. Statistical Analysis Methods

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

12.4.1. General Considerations

Data will be summarized by treatment group. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, 25% and 75% percentiles, and minimum and maximum values.

There are two stratification factors for randomization: country and ECOG performance status (0-1 versus 2). A randomization schema will be in place to ensure the best possible balance of treatment assignment within each stratum produced by these stratification factors. Countries will be grouped into the factor of "region" with 3 components: US, Europe, and Asia. The factor "region" will be used instead of "country" in the statistical analysis models to account for regional differences in clinical practice. Unless otherwise specified, ECOG status as entered in IWRS at the time of randomization will be used as the factor for all stratified analyses.

12.4.2. Patient Disposition

Patient disposition will be summarized for all patients by treatment group and overall. The summary will include number of all screened patients, and number and percentage of patients who were randomized, received study drug, discontinued from the study drug with the reasons, and discontinued from study with the reasons.

12.4.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the ITT population by treatment group and overall. The demographics to be summarized include age, age group (<65 versus ≥65 years old), gender, race, ethnicity, and region. The baseline characteristics to be summarized include ECOG status, NSCLC history (date of diagnosis, histologic type, and prior therapies by line (eg, surgery, radiation, systemic chemotherapy, or immunotherapy). In addition, the recorded PD-L1 status at the screening visit will also be summarized along with vital signs at the screening visit (body weight, body mass index [BMI], BSA).

12.4.4. Prior and Subsequent Anticancer Therapies

Prior and subsequent anticancer therapy verbatim terms will be coded to Anatomical Therapeutic Classification (ATC) and preferred term (PT) using the latest version of World Health Organization-Drug Dictionary (WHO-DD) for the ITT population. Summary statistics will be provided for prior systemic anti-cancer therapies given in different setting (1st line or 2nd line) by treatment group and overall. For the subsequent systemic anti-cancer therapies, the lines of therapy, response to each treatment regimen, and disease progression status will also be summarized by treatment group and overall.

12.4.5. Study Drug Exposure, Modification and Dose Intensity

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

Duration of study drug exposure will be calculated for docetaxel and for trilaciclib/placebo by treatment group.

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

Study drug modifications will be summarized by treatment group in three categories: chemotherapy dose reductions, chemotherapy cycle delay, and infusion interruption. The number and percentage of patients who have at least one dose reduction for docetaxel will be summarized along with a summary of the number of dose reductions that have occurred; 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/placebo or docetaxel will be summarized along with a summary of the number of interruptions. Lastly, the primary reason for each form of study drug modification (docetaxel dose reduction, cycle delay, and infusion interruption) will also be summarized by treatment group.

For trilaciclib/placebo and docetaxel, respectively, cumulative dose, dose intensity, relative dose, and relative dose intensity will be derived and summarized by treatment group.

12.4.6. Efficacy Analyses

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

12.4.6.1. Analyses of Primary Efficacy Endpoint – Overall Survival

The primary endpoint OS is defined as the time (months) from the date of randomization to the date of death for patients who died in the study due to any cause, and the time to the last contact date known to be alive for those who survived as of the data cutoff date for the interim OS analysis or as of the date when the study database is locked for the final analysis (censored cases). Patients lacking data beyond the date of randomization will have their survival time censored at the date of randomization.

The targeted number of deaths for the final analysis in 104 and the final analysis for OS is event-driven. The number and percentage of patients who died or censored will be summarized by treatment group along with the reason for death.

Treatment effect on OS will be primarily evaluated using a stratified log-rank test controlling for the stratification factors of region (US, Europe, or Asia) and ECOG performance status (0-1 versus 2). The magnitude of the treatment effect, HR (trilaciclib versus placebo), will be estimated using a Cox proportional hazard model with the same factors as included in the stratified log-rank test. At the final analysis, the (1-α)*100% confidence interval (CI) will be generated for the HR, where the α is a 2-sided statistically significant level to be used for the final OS analysis determined by actual information fraction used at the interim and the O'Brian-Fleming α-spending function.

For each treatment group, the Kaplan-Meier plot will be generated, and the median, 25% and 75% percentile of OS will be estimated using the Kaplan-Meier method with their corresponding 95% confidence interval calculated using the method by Brookmeyer and Crowley (1982). Additionally, Kaplan-Meier estimates will be provided for the survival probability along with their two-sided 95% CIs (Kalbfleisch, 1980) at selected landmarks of 6, 12, 18, and 24 months.

12.4.6.1.1. Interim Analysis for Overall Survival

An interim analysis of OS will be conducted at the 70% information fraction, that is, when 73 deaths are observed. The timing of the interim analysis is estimated to be approximately 19 months after the first patient is randomized in the study. O'Brien-Fleming method for α-spending is applied to ensure strong control family-wise Type I error rate of 1-sided of 0.025 between the interim and the final analysis for OS. At the interim analysis, the significant treatment effect of trilaciclib compared with placebo for OS is established if the 1-sided p-value from the stratified log-rank test is less than or equal to 0.0075 (Table 13). If the final analysis is performed at 104

cumulative deaths as planned, a 1-sided significance level of 0.0227 will be used to evaluate treatment effect for OS at the final analysis. The actual significance level at the final analysis for OS will be re-calculated if the actual information fraction for the interim OS analysis is different than the planned 0.70 using the O'Brien-Fleming α-spending function.

There will be no final OS analysis if the superiority of trilaciclib over placebo for OS is established at the interim analysis.

Table 13: Thresholds for Claiming Statistical Superiority (Trilaciclib versus Placebo) at Interim or Final Analysis for Overall Survival

Analysis	# of Deaths	Analysis Timing from FPI (month)[a]	Z-scale	HR-scale	P-value Scale (1-Sided)
Interim Analysis	73	19	2.434	0.562	0.0075
Final Analysis[b]	104	30	2.000	0.673	0.0227

FPI=first patient randomized; HR=hazard ratio.

[a] Estimated based on the assumptions of accrual period and duration of follow up as used in the sample size calculation.

[b]Statistical criteria judging the significance at the final analysis could be re-calculated if the interim analysis information fraction is different than 0.70.

The aforementioned analyses will be conducted on the ITT population.

12.4.6.2. Analysis for Secondary Anti-tumor Efficacy Endpoints

Secondary anti-tumor endpoints include the following:

- Progression free survival (PFS)
- Objective response rate (ORR)
- Duration of objective response (DOR)

Progressive disease (PD) and tumor response status are derived per RECIST v1.1 based on tumor assessment data entered into the EDC by Investigators.

12.4.6.2.1. Analysis for Progression Free Survival

Progression free survival is defined as the time (months) from date of randomization to the date of documented radiologic PD per RECIST v1.1 or date of death regardless the cause, whichever comes first. PFS will be determined using all available data up to 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 earliest. Censoring rules for patients who do not experience PD or death at the data cutoff date or at the date for final database lock will be detailed in the study SAP.

The treatment effect on PFS will be evaluated by using a stratified log-rank test controlling for the two stratification factors. A Cox proportional hazard model with the same terms as in the stratified log-rank test will be used to estimate the HR (trilaciclib versus placebo) for PFS along with its 95% confidence interval. In addition, Kaplan-Meier plots will be generated and the

median, 25% and 75% percentile of PFS will be estimated using the Kaplan-Meier method by treatment group with their corresponding 95% confidence interval calculated using the method by Brookmeyer and Crowley (1982).

Per literature, the expected median PFS for patients receiving docetaxel is 3 months (Garon, 2014). Assuming trilaciclib can achieve a treatment effect of HR of 0.60, it is estimated that 86% of patients would have a radiographic disease progression or died at the time when OS interim analysis is performed. Therefore, the analysis for PFS will be conducted at the time of performing interim OS analysis. However, if the observed PD or deaths at the date of data cutoff for the OS interim analysis is less than 80%, the final PFS will be performed using the final database if the study is not stopped for success after the interim OS analysis. In that event, the treatment effect for PFS as observed at the final analysis will be considered to be primary.

PFS will be analyzed on the ITT population.

12.4.6.2.2. Analysis for Tumor Response Status and Duration of Objective Response

At each tumor assessment visit, an overall time point response per RECIST v1.1 will be determined programmatically using the measurements of target lesions, non-target lesions, and new lesions entered to the eCRF by the Investigators. Best overall response (BOR) will be determined per RECIST v1.1 using all timepoint 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 earliest. The BOR status for patients will be summarized by the number and percentage of patients in each of the following categories: complete response (CR) (confirmed), partial response (PR) (confirmed), stable disease (SD) and Not Evaluable (NE).

ORR is defined as the proportion of patients with confirmed CR or confirmed PR as the BOR status. ORR along with its exact 95% two-sided confidence interval using the Clopper-Pearson method will be computed for each treatment group. The treatment group difference for ORR will be evaluated using a stratified Cochran–Mantel–Haenszel (CMH) test accounting for the two stratification factors. The adjusted proportion difference (trilaciclib minus placebo) and its 95% CI will be calculated using CMH weight (Kim, 2013).

DOR is the time (months) from the first date when CR or PR was achieved and confirmed in the next tumor scan to the date when the patient experienced disease progression or died in the absence of PD. For those who achieved objective response status and did not have disease progression or death at the time of data analysis, the earliest date of the following, if it exists, will be used to calculate censored time: (i) withdrew consent to obtain scans; (ii) last contact; (iii) initiated subsequent anticancer therapy; otherwise, the censored DOR will be calculated using the last date known with retained response status as of the data cutoff date for the analysis. DOR will be analyzed for the patients who have achieved objective response. The Kaplan-Meier method will be used to estimate the median, 25% and 75% percentile of DOR by treatment group, along with the 95% CI calculated using the method by Brookmeyer and Crowley (1982).

Analyses for ORR and DOR will be based on the Response Evaluable patient population.

12.4.6.3. Analysis for Myelosuppression Endpoints

Myelosuppression endpoints are grouped by lineage and consequence of CIM as follows.

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

12.4.6.3.1. Analysis for DSN in Cycle 1

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

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

12.4.6.3.2. Analysis for Binary Myelosuppression Endpoints

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

12.4.6.3.3. Analysis for Counting Myelosuppression Endpoints

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

12.4.6.4. Subgroup Analysis for Primary Efficacy Endpoint

Treatment effect for the primary endpoint OS will be evaluated for each of the stratification factors: Region (US, Europe, or Asia) and ECOG status (0-1 versus 2). The treatment effects in each category of a factor will be evaluated by using a stratified log-rank test controlling for the other stratification factor. A Cox proportional hazard model with the same terms as used in the stratified log-rank test will be employed to estimate the HR and its 95% CIs within each category of the factor. A forest plot for the HR of OS and its 95% CI will be produced.

Subgroup analysis will be conducted for some baseline characteristics that might have impact on the treatment effect for OS and the details will be specified in the study SAP.

12.4.7. PRO Analyses

The EORTC QLQ-C30, EORTC QLQ-LC13 with supplemental weight loss item (EORTC IL118), FACIT-Fatigue, EQ-5D-5L, PGIC, and PGIS instruments will be used to collect the quality-of-life data to assess the impact of trilaciclib on various quality of life measures compared with placebo. Analysis for the variables derived from these questionaries will be based on the ITT population and detailed in the study SAP.

12.4.8. Safety Analyses

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

12.4.8.1. 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 (SOC) and PT using the latest version of MedDRA. The severity (toxicity grades 1-5) of AEs will be graded according to the

NCI-CTCAE v5.0 by Investigators. The number and percentage of patients experiencing any AEs will be summarized overall and tabulated by SOC, PT and CTCAE grade for each treatment group. AEs considered by the Investigator to be related to a study drug, AEs leading to study drug discontinuation or dose modifications, and trilaciclib AESIs will be summarized by SOC, PT and CTCAE grade, when appropriate. In the tabulation of severity and causality of an AE, if the same AE occurred on multiple occasions, the highest grade of toxicity and strongest relationship to the study drug will be used in a summary.

12.4.8.2. Other Safety Endpoints

Observed values and changes from baseline to each end of the cycle, the maximum and minimum values during the treatment period in vital signs, and ECG intervals, and laboratory assessments of hematology, serum chemistry, and liver function parameters will be summarized by treatment group.

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

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

[redacted]

12.4.10. Pharmacokinetic Analyses

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

The pharmacokinetics of docetaxel will also be determined using a non-linear mixed effects modeling approach. Relevant population pharmacokinetic parameters will be estimated and reported. Details of population pharmacokinetic analyses will be described in the population pharmacokinetic/pharmacodynamic analysis plan.

12.4.11. Pharmacokinetic/Pharmacodynamic Analyses

[redacted]

Details of population PK/pharmacodynamic analyses will be described in a separate population PK/pharmacodynamic analysis plan.

13. ETHICS

13.1. Ethics Review

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

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

The Investigator will be responsible for the following:

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

13.2. Ethical Conduct of the Study

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

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

13.3. Written Informed Consent

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data Protection

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

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

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

14.2. Data Quality Assurance

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

relating to the study, the Investigator must permit access to such records. No records may be destroyed during the retention period without the written approval of the Sponsor. No records maybe transferred to another location or party without written notification to the Sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained. However, if required by local regulation that these documents should be retained for a longer period, then Retention of Documentation will abide by local regulation.

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

14.3. Dissemination of Clinical Study Data

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

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

14.4. Source Documents

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

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

14.5. Audits and Inspections

Authorized representatives of G1 Therapeutics, Inc., 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, Inc. immediately if contacted by a regulatory agency about an inspection.

15. PUBLICATION POLICY

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

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

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17. APPENDICES

17.1. Clinical Laboratory Tests

- The timing and laboratory tests detailed in Schedule of Assessments (Table 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 14: 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; RBC=red blood cell; WBC=white blood cell; WOCBP=woman of childbearing potential

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

17.2.1. Definition of AE

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

17.2.2. Definition of SAE

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

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

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

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to G1 Therapeutics, Inc. (or designee) in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by G1 Therapeutics, Inc. (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, Inc. (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, Inc. PVG (or designee) within 24 hours of notification on an SAE Form in the eCRF. Any relevant source data related to the SAE that cannot be entered in the EDC should be emailed or faxed to G1 Therapeutics, Inc. PVG (or designee):

  G1 Therapeutics, Inc. 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, Inc. PVG (or designee). However, it is very important that the Investigator always make an assessment of causality (Not Related or Related) for every event before the initial transmission of the SAE data to G1 Therapeutics, Inc. PVG (or designee). • The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by G1 Therapeutics, Inc. PVG (or designee) to elucidate the nature and/or causality of the SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any new or updated SAE data to G1 Therapeutics, Inc. PVG (or designee) within 24 hours of receipt of the information: **G1 Therapeutics, Inc. Pharmacovigilance** **Email: safetyreporting@g1therapeutics.com** **Fax: +1-984-285-7131**

17.2.4. Reporting of SAEs

SAE Reporting to G1 Therapeutics, Inc. (or designee) via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to G1 Therapeutics, Inc. (or designee) will be the EDC. • If the electronic system is unavailable, then the site will use the paper SAE Report Form in order to report the event within 24 hours via email or fax (see below for SAE reporting contact information). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site should report this information on a paper SAE Report form or notify the Medical Monitor by telephone. • Contact for SAE reporting: **G1 Therapeutics, Inc. 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 6 months following discontinuation of treatment.

- Female patients: All females of childbearing potential must have a negative serum β-hCG test result at Screening, and negative serum or urine pregnancy test at each cycle during treatment and at the Post Treatment Visit (see Section 11.3.5 and Table 6).

- 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, Inc. 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, Inc. 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, Inc. 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, Inc. PVG or designee. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention.
- Contact for Pregnancy reporting:

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

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

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

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

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

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

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

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

Evaluation of Target Lesions

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

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

Appearance of New Lesions

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

Timepoint Response

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

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

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

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

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

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

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