Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer

Clinical Study Protocol G1T28-05
EudraCT # 2017-000358-20

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Investigational Phase: 2

Sponsored by:
G1 Therapeutics
79 T.W. Alexander Drive
4501 Research Commons, Suite 100
Research Triangle Park, NC 27709
[redacted]

SPONSOR: G1 THERAPEUTICS

I have read and understand the contents of this clinical protocol for Study G1T28-05 dated 14 September 2018 and I agree to meet all obligations of the sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the principal investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Approved by:

[redacted]

Date

[redacted]

G1 Therapeutics

PROTOCOL SIGNATURE PAGE

Clinical Study Protocol G1T28-05: Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated Extensive Stage Small Cell Lung Cancer

Original Protocol (Version 1.0) Issue Date: 14 February 2017

Version: 2.0 (Amendment 1) dated 02 May 2017

Version: 3.0 (Amendment 2) dated 14 September 2018

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

Principal Investigator:

Principal Investigator Signature	Date
Principal Investigator Name	Institution

1. TABLE OF CONTENTS

1.1. List of In-Text Tables

1.2. List of In-Text Figures

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ARR	adjusted relative risk
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	anti-atezolizumab therapeutic antibodies
ATC	Anatomical Therapeutic Classification
ATIN	acute tubulo-interstitial nephritis
AUC	area under the concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from 0 to t hours after dosing
$AUC_{0-\infty}$	area under the concentration time curve from time zero extrapolated to infinity
AUC_{EOC}	area under the concentration-time curve from predose to end of cycle
AUC_{Nadir}	area under the concentration-time curve from predose to nadir
AUC_{NEOC}	area under the concentration-time curve from nadir to end of cycle
BCRP	breast cancer resistance protein
BED	biologically effective dose
β-hCG	beta human chorionic gonadotropin
bpm	beats per minute
BSA	body surface area
BSEP	bile salt export pump
BUN	blood urea nitrogen
CBC	complete blood count
CD3	cluster of differentiation 3
CD137	cluster of differentiation 137
CDK2/4/6	cyclin-dependent kinase 2/4/6
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance

Abbreviation	Definition
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D5W	dextrose 5% in water
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EdU	5-ethynyl-2'-deoxyuridine
EEG	electroencephalogram
EOI	end of infusion
E/P	etoposide and carboplatin
E/P/A	etoposide, carboplatin, and atezolizumab
ESA	erythropoietin stimulating agent
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FDG-PET	positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose
FSH	follicle-stimulating hormone
G1	gap 1 phase of the cell cycle
G2	gap 2 phase of the cell cycle
G1T28	trilaciclib; formerly G1T28-1
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus

Abbreviation	Definition
HIV	human immunodeficiency virus
HR	hazard ratio
HSC	hematopoietic stem cell
HSPC	hematopoietic stem and progenitor cell
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	interferon-gamma
IHC	immunohistochemistry
IL-2	interleukin-2
irAE	immune-related adverse event
irCR	immune-related complete response
irPD	immune-related disease progression
irPFS	immune-related progression-free survival
irPR	immune-related partial response
IRB	institutional review board
IRR	infusion-related reaction
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irSD	immune-related stable disease
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web-response system
LD	longest diameter
LDH	lactate dehydrogenase
LS	least squares
M	mitosis phase of cell cycle
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
MDR1	p-glycoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOA	mechanism of action
MRI	magnetic resonance imaging
MRP1 or 2	multidrug resistance protein 1 or 2
mUC	metastatic urothelial carcinoma
NCI	National Cancer Institute
NCI-H69	human small cell lung cancer cell line

Abbreviation	Definition
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
PCI	prophylactic cranial irradiation
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
[redacted]	[redacted]
[redacted]	[redacted]
qRT-PCR	quantitative reverse transcriptase-polymerase chain reaction
Rb	retinoblastoma protein
RB-1	retinoblastoma gene
RBC	red blood cell(s)
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RH	relative humidity
RNA	ribonucleic acid
S	synthesis phase of cell cycle in which DNA is replicated
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SMQs	standardised MedDRA queries
SOC	system organ class
StD	standard deviation
$t_{1/2}$	terminal half-life
T3	tri-iodothyronine
T4	thyroxine

Abbreviation	Definition
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
TOP	trilaciclib, oxaliplatin/anti-PD-L1 combination
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UC	urothelial carcinoma
UGT1A1	uridine disphosphate glucuronosyltransferase 1 family, polypeptide A1
ULN	upper limit of normal
Vz	volume of distribution in the terminal elimination phase
WHO-DD	World Health Organization Drug Dictionary
WBC	white blood cell
WHO	World Health Organization

3. SYNOPSIS

Title	Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer
Study Rationale	Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases worldwide and more than two-thirds of patients present with extensive-stage disease. Although response rates to first-line chemotherapy in extensive-stage SCLC are in the range of 50% to 60%, the median duration of response is short (approximately 4 months), with a median survival of 8 to 10 months and 2-year survival rates of less than 10%. Increasing evidence suggests that immune responses against SCLC cells make immunotherapy a viable therapeutic approach in this disease. Furthermore, there is evidence that certain chemotherapeutic regimens may augment the immunotherapeutic response in SCLC, in part by releasing neoantigens and educating the immune system against the surviving cancer cells. Atezolizumab (Tecentriq®), is a monoclonal antibody that binds to programmed death-ligand 1 (PD-L1), inhibiting its interaction with the programmed cell death protein 1 (PD-1) receptor and releasing the PD-L1/PD-1 mediated inhibition of the immune response. Atezolizumab is an immunotherapy indicated for the treatment of locally advanced or metastatic urothelial carcinoma (approved in the United States in May 2016) and metastatic non-small cell lung cancer (NSCLC) (approved in the United States in October 2016). Etoposide and carboplatin (E/P) is a standard SCLC treatment and is currently under investigation with atezolizumab for the treatment of SCLC. The major drawback to platinum-based chemotherapeutic regimens used in SCLC treatment is dose-limiting myelosuppression, which may antagonize the intended effects of the immunotherapy by reducing both the number and function of lymphocytes. Therefore, an approach to maintain immune system function while administering cytotoxic chemotherapy is needed to fully realize the therapeutic potential of immunotherapies. Trilaciclib (G1T28) is a highly potent, selective, and reversible cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in development to preserve bone marrow and immune system function (including lymphoid progenitors and lymphocytes) from damage by chemotherapy, allowing faster hematopoietic recovery, preserving long-term bone marrow function, and enhancing the antitumor activity of chemotherapy. Trilaciclib is administered intravenously prior to every dose of chemotherapy in every cycle, eg, on Days 1 to 3 prior to E/P administration in 21-day cycles, for extensive-stage SCLC. This pulsatile dosing around chemotherapy administration allows preservation of the bone marrow and immune system without adding to the chemotherapy-induced myelosuppression caused by chronic inhibition of CDK4/6 in the bone marrow. To evaluate the effect of trilaciclib in combination with chemotherapy and

	an immune checkpoint inhibitor, immunocompetent MC38 tumor-bearing mice were treated with trilaciclib, oxaliplatin, or anti-PD-L1 alone or in combination, and tumor size was measured during and after treatment for 100 days. The addition of trilaciclib to an oxaliplatin/anti-PD-L1 combination (TOP) treatment significantly improved the overall response rate, complete response rate, and median overall survival (OS) compared to oxaliplatin/anti-PD-L1 combination (93% vs 46%; 79% vs 38%; not reached at 100 days vs 59 days, respectively). Taken together, this demonstrates that trilaciclib, which has been shown to preserve immune function during chemotherapy, enhances the antitumor activity of chemotherapy/anti-PD-L1 combination therapy. In summary, nonclinical data demonstrate that trilaciclib administration with chemotherapy preserves bone marrow and immune system function from damage by chemotherapy and enhances the antitumor activity of chemotherapy/anti-PD-L1 combination therapy. Additionally, preliminary clinical data suggest that lymphocyte numbers are relatively unchanged when trilaciclib is used in combination with chemotherapy. Preserving adaptive immunity with trilaciclib may enhance the efficacy of chemotherapy combined with immune checkpoint inhibitors, supporting clinical testing of the novel combination of etoposide, carboplatin, and atezolizumab (E/P/A) therapy and trilaciclib.
Clinical Phase	2
Indication	Treatment of SCLC

Objectives	**Primary Objectives**
	Evaluate the potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression in patients with SCLC undergoing treatment with E/P/A
	Key Secondary Objectives
	Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A
	Supportive Secondary Objectives
	Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A
	Evaluate the antitumor activity of trilaciclib or placebo administered in combination with E/P/A to patients with SCLC
	Determine the safety and tolerability of trilaciclib or placebo administered in combination with E/P/A in patients with SCLC
	Evaluate potential of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing effects on multiple lineages and current standard of care interventions to treat myelosuppression (neutrophils, RBC, platelets, lymphocytes)
	Describe the PK of trilaciclib, carboplatin, and etoposide in a subset of patients; and atezolizumab in all patients
	[redacted]
	ATA = anti-atezolizumab therapeutic antibodies; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; E/P/A = etoposide/carboplatin/atezolizumab; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; [redacted] RBC = red blood cells; SCLC = small cell lung cancer
Study Design	This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study of the efficacy and safety of E/P/A with trilaciclib or placebo therapy for patients with newly diagnosed extensive-stage SCLC. Approximately 100 patients will be randomly assigned (1:1 fashion) to trilaciclib or placebo administered intravenously on Days 1 to 3 with E/P/A therapy for up to four 21-day cycles (induction part). Following the completion of up to 4 chemotherapy-containing (trilaciclib or placebo +

E/P/A) cycles, patients will proceed to the maintenance part of the study and receive atezolizumab every 21 days. Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part. Treatment in both parts will continue until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit. The study includes 3 phases: Screening Phase, Treatment Phase (induction part + maintenance part), and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes after the last Post-Treatment Visit.

Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no).

Criteria for Subsequent Cycles and Study Duration

Study drug administration will continue for up to 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles during the induction part of the study and atezolizumab will be administered every 21 days during the maintenance part of the study. Study drug administration will continue until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. However, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons as described below.

In order to start Induction Cycle 2 and subsequent cycles as scheduled during the induction part, patients must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline. A delay of > 9 weeks for recovery from any toxicity related to trilaciclib or placebo + E/P in order to meet the continuation criteria will result in discontinuation of trilaciclib or placebo + E/P. A delay of > 15 weeks for recovery and management of immune-related toxicities attributed to atezolizumab (12 weeks for recovery to $\leq$ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to $\leq$ 10 mg/day) will result in discontinuation of atezolizumab. If patients meet the criteria for starting the subsequent cycle, a delay of up to 2 weeks is permitted for administrative reasons (eg, holiday, vacation, etc.); however, a total delay of more than 9 weeks for trilaciclib or placebo + E/P, or 15 weeks for atezolizumab must be discussed with the medical monitor. If the subsequent cycle is delayed, the patient should still complete the clinical laboratory assessments, the Functional Assessment of Cancer Therapy–Lung quality of life instrument (FACT-L), and the Functional Assessment of Cancer Therapy–Anemia quality of life instrument (FACT-An) questionnaires on the scheduled

Day 1, as well as on the actual first dosing day of the next cycle.

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs); immune-related hepatitis, pneumonitis, colitis, pancreatitis; diabetes mellitus; hypothyroidism; hyperthyroidism; adrenal insufficiency; Guillain-Barré syndrome; myasthenic syndrome or myasthenia gravis; hypophysitis; and meningoencephalitis. In addition, systemic immune activation is a potential risk associated with atezolizumab when given in combination with other immunomodulating agents. Refer to the Atezolizumab Guidance for the Investigator (Appendix 1) for a detailed description of anticipated safety risks for atezolizumab and their management.

Management of immune-related adverse events (irAEs) attributed to atezolizumab may include administration of immunosuppressant medications like corticosteroids, etc.; delay of a scheduled dose; or discontinuation of therapy. No dose reductions will be allowed for atezolizumab. Atezolizumab dosing will be held in the event of any irAEs attributed to atezolizumab until the event has improved to ≤ Grade 1. See the Atezolizumab Guidance for the Investigator (Appendix 1).

Other irAEs attributed to atezolizumab not listed above should be assessed by the investigator and discussed with the medical monitor to determine if atezolizumab should be held or discontinued. If the irAE does not improve to ≤ Grade 1 within 12 weeks, treatment will be permanently discontinued.

Discontinuation or interruption of trilaciclib or placebo + E/P does not preclude continuation of atezolizumab and vice versa. For instance, if an adverse event (AE) is attributed to trilaciclib or placebo, etoposide, or carboplatin (eg, hematologic toxicity) during the induction part of the study, then atezolizumab will be continued while the trilaciclib or placebo + E/P are held. While the trilaciclib or placebo + E/P are held, the patient will continue to receive atezolizumab, be monitored for safety, and will begin the next trilaciclib or placebo + E/P/A-containing induction cycle after the toxicity resolves. If the AE is immune related and attributed to atezolizumab; then trilaciclib or placebo + E/P will be continued for up to 4 cycles while the atezolizumab is held. After discontinuation of all study drugs, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, [redacted] complete blood count (CBC) assessment on Day 22; all Post-Treatment Visits; and the Survival Follow-up Phase of the study, which is to continue until at least 70% of the patients on the study have died. The G1T28-05 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study.

Tumor Assessment

Tumor assessments using radiologic imaging will be performed after every even cycle for the first 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug. Tumor assessments will include tumor response based on RECIST v1.1 and irRECIST. For tumor assessment, all sites of disease should be assessed radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) at

	screening and every scheduled tumor assessment until the occurrence of disease progression. CT or MRI scans obtained as standard of care prior to informed consent will not need to be repeated if performed within 14 days prior to dosing. Brain scans performed as standard of care prior to informed consent will not need to be repeated if performed within 28 days prior to dosing. Assessments should be performed within 7 days prior to starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. For patients who have a confirmed CR, it is strongly recommended that they receive prophylactic cranial irradiation (PCI) after completion of chemotherapy (ie, induction). Patients with a confirmed PR should also consider PCI after completion of chemotherapy (ie, induction) based on the investigator's judgment. Following the completion of the induction part, PCI may be administered concurrently with atezolizumab during the maintenance part. For those patients who have not progressed at the time of study drug discontinuation, tumor assessments to include all sites of disease will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography (PET) is used, it should also be accompanied by spiral CT or MRI. **Safety Assessments** Safety assessments will include monitoring of AEs (including SAEs, irAEs, and AEs of special interest [AESI]), vital signs measurements, physical examinations, electrocardiograms (ECGs), performance status, clinical laboratory studies, and IRRs. Safety surveillance reporting of AEs commences at the time of informed consent. AEs will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug. An independent data monitoring committee (DMC) will monitor accumulating safety and disposition data after approximately 12 patients have been enrolled and have completed at least 1 cycle to assess the initial safety data from the 2 groups, and then approximately every 4 months during the Treatment Phase of the study, depending upon the enrollment rate. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.
Treatment Duration	Study drug administration will continue for each patient until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. However, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit. Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part.

Study Duration	The total study duration is at least 36 months, assuming 12 months of accrual and 24 months follow-up. The Survival Follow-up Phase will continue until at least 70% of the randomized patients have died.
Approximate Number of Patients	Approximately 100 patients will be randomly assigned to 1 of 2 groups as follows: trilaciclib administered intravenously (IV) with E/P/A therapy during induction followed by atezolizumab maintenance (Group 1) or placebo administered IV with E/P/A therapy during induction followed by atezolizumab maintenance (Group 2).
Number of Study Centers	Up to 60 centers in North America and Europe
Diagnosis and Main Criteria for Inclusion	For a patient to be eligible for participation in this study, all of the following criteria must apply. 1. Age ≥ 18 years 2. Unequivocally confirmed diagnosis of SCLC by histology or cytology, preferably including the presence of neuroendocrine features by immunohistochemistry 3. Extensive-stage SCLC 4. At least 1 target lesion that is measurable by RECIST v1.1 (Eisenhauer 2009) 5. Hemoglobin ≥ 9.0 g/dL 6. ANC ≥ 1.5×10^9/L 7. Platelet count ≥ 100×10^9/L 8. Creatinine ≤ 1.5 mg/dL or glomerular filtration rate (GFR) of ≥ 60 mL/minute 9. Total bilirubin ≤ 1.5 × ULN; < 3 × ULN if the patient has documented Gilbert's disease 10. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases 11. ECOG performance status of 0 to 2 12. Predicted life expectancy of ≥ 3 months 13. Contraception: a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening. Females must be either postmenopausal, surgically sterile, or agree to use 2 forms of highly effective contraception during the study and for 6 months following discontinuation of study treatment i. Postmenopausal is defined as (1) at least 60 years of age, (2) medically confirmed ovarian failure, or (3) younger than 60 years of age and have had cessation of regular menses for at least 12 consecutive months with no

alternative pathological or physiological cause, and/or serum levels of estradiol and follicle stimulating hormone within the laboratory's reference range for postmenopausal females

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

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

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

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

14. Able to understand and sign an informed consent

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

1. Limited-stage SCLC
2. Prior chemotherapy for limited or extensive-stage SCLC
3. Prior treatment with immunotherapies including but not limited to cluster of differentiation 137 (CD137) agonists or immune checkpoint blockade therapies (such as anti-program cell death protein 1 [PD-1], or anti-programmed death ligand 1 [PD-L1], CTLA4 therapeutic antibodies)
4. Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids
5. Malignancies other than SCLC within 3 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome
6. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan (history of radiation pneumonitis in the radiation field [fibrosis] is permitted)
7. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Exceptions include vitiligo, controlled asthma, Type I diabetes, Graves' disease, Hashimoto's disease, or with medical monitor approval. Stable replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) for well-controlled disease is not considered a form of systemic treatment
8. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (Class III or IV as defined by the New York Heart Association [NYHA] functional classification system)
9. Known history of stroke or cerebrovascular accident within 6 months prior to enrollment
10. Serious active infection at the time of enrollment
11. Psychiatric illness/social situations that would limit study compliance
12. Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol
13. Known human immunodeficiency virus (HIV), known active Hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive or HBV DNA detected) or Hepatitis C (eg, hepatitis C virus [HCV] RNA [qualitative] is detected)
14. Radiotherapy to any site within 2 weeks prior to enrollment
15. Receipt of any investigational medication within 4 weeks prior to enrollment
16. Administration of a live attenuated vaccine within 4 weeks before

	enrollment or anticipation that such a live attenuated vaccine will be required during the study 17. Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (eg, FluMist) within 4 weeks prior to enrollment, at any time during the study, and at least 5 months after the last dose of atezolizumab 18. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. 19. Hypersensitivity to any of the components of the formulation of etoposide or etoposide phosphate 20. Hypersensitivity to carboplatin or other platinum-containing compounds, or mannitol 21. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins 22. Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies 23. Legal incapacity or limited legal capacity 24. Pregnant or lactating women
Chemotherapy Treatment	Carboplatin dose calculated using the Calvert formula with a target area under the concentration-time curve (AUC) = 5 (maximum dose of 750 mg) administered IV over 30 minutes on Day 1, and 100 mg/m^2 etoposide administered IV over 60 minutes daily on Days 1, 2, and 3 of 21-day cycles.
Investigational Medicinal Products and Administration	Trilaciclib 240 mg/m^2 in 250 mL of dextrose 5% in water (D5W) or in sodium chloride solution 0.9%, administered as an IV infusion over approximately 30 minutes once daily on Days 1 to 3 of each 21-day cycle prior to the dose(s) of chemotherapy. Atezolizumab 1200 mg in 250 mL sodium chloride solution 0.9% will be administered as an IV infusion on Day 1 of each 21-day cycle in both the induction and maintenance parts. During the induction part, atezolizumab should be administered following the completion of trilaciclib or placebo, carboplatin, and etoposide. Atezolizumab should be infused over 60 minutes for the first administration and, if tolerated, all subsequent infusions may be delivered over 30 minutes. There will be no intrapatient dose modifications of trilaciclib or atezolizumab in the study.

Comparator Dosage and Administration	Placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% administered as an IV infusion over approximately 30 minutes once daily on Days 1 to 3 of each 21-day cycle prior to the dose(s) of chemotherapy.
Efficacy Evaluation	Efficacy evaluation will be based on tumor response using RECIST v1.1, including ORR, PFS, and OS. Additionally, tumor response and immune-related progression-free survival (irPFS) will be assessed using irRECIST.
Safety Evaluation	Safety will be assessed by evaluation of AEs (including serious adverse events [SAEs], irAEs, and AESI) physical examinations, performance status, vital sign measurements, ECGs, clinical laboratory data, and IRRs. Anti-atezolizumab therapeutic antibodies (ATA) will be measured in all patients in each treatment group prior to infusion on Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 and 90 days after the last dose of study drug.
Pharmacokinetics Evaluation	In a subgroup of at least 5 patients in each treatment group of the study, blood samples will be collected for the measurement of trilaciclib, etoposide, and carboplatin concentrations in plasma as described below: <u>Day 1 of Induction Cycles 1 and 3:</u> Blood samples will be collected at the following time points relative to the start of trilaciclib or placebo infusion on Day 1 of Induction Cycles 1 and 3 for patients enrolled in the PK subgroup of the study: predose (0 hour; prior to dosing of trilaciclib or placebo) and at 0.5 (end of infusion [EOI] of trilaciclib or placebo), 1 (EOI of carboplatin), 2 (EOI of etoposide), 4, 6, and 24 (prior to trilaciclib or placebo dose on Day 2) hours. The EOI sample for trilaciclib or placebo should be drawn 2 to 5 minutes prior to the EOI. All patients in each treatment group will have blood samples collected for the measurement of atezolizumab plasma concentrations as below: <u>Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and Every Eighth Cycle Thereafter; and at 30 and 90 Days After the Last Dose of Study Drug:</u> Blood samples will be collected at the following time points relative to atezolizumab infusion to determine the minimum and maximum observed serum atezolizumab concentration: predose and 30 minutes after the end of the atezolizumab infusion. Pharmacokinetic (PK) parameters (eg, C_{max}, minimum concentration [C_{min}], time to reach C_{max} [T_{max}], AUC_{0-t}, $AUC_{0-\infty}$, terminal half-life [$t_{1/2}$], volume of distribution in the terminal elimination phase [V_z], and CL) will be derived from trilaciclib, etoposide, carboplatin, and atezolizumab plasma concentration-time data, as appropriate.
[redacted]	[redacted]
Immunologic Marker Assessment	Peripheral blood samples will be collected at predose on Day 1 of Induction Cycle 1, Day 1 of Maintenance Cycle 1 (first cycle of maintenance part), Day 1 of Maintenance Cycle 5; and at the 90 Day Post-Treatment Visit.

Statistical Analysis	The intent-to-treat (ITT) population includes all randomized patients and will be the primary analysis set for efficacy and [redacted]. ITT analyses will be conducted on the basis of the assigned treatment. The safety analysis set includes all patients who received at least 1 dose of study drug and will be used for the analysis of safety endpoints. The safety analysis set analyses will be conducted on the basis of the actual treatment received. The PK analysis set will include all dosed patients in the PK portion of the study with evaluable PK data. Data will be summarized by treatment group. Treatment differences between treatment groups will be calculated as trilaciclib + E/P/A therapy versus placebo + E/P/A therapy. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, and minimum and maximum values. Study G1T28-05 was originally designed as a Phase 2 clinical study to investigate if myelopreservation, ie, preservation of hematopoietic stem and progenitor cell (HSPC) and immune system function during chemotherapy, by trilaciclib could provide survival benefit to patients receiving a combination of cytotoxic chemotherapy and an immune checkpoint inhibitor. Recent results from a clinical study in treatment-naive extensive-stage SCLC patients (Study G1T28-02) who received trilaciclib or placebo in combination with etoposide/carboplatin, provided compelling evidence that trilaciclib resulted in a clinically meaningful decrease in myelosuppression across 3 lineages: neutrophils, RBC, and lymphocytes. Hence, the primary analysis in this Study G1T28-05, where the chemotherapy backbone of etoposide and carboplatin is the same as Study G1T28-02, is being modified to assess primary and key secondary myelosuppression efficacy endpoints. This allows for an earlier assessment of trilaciclib's mechanism of action (MOA) and efficacy, with OS retained as a secondary endpoint. This change in endpoints does not alter the assessments or protocol-defined patient care. The primary endpoints include (i) duration of severe (Grade 4) neutropenia in Cycle 1 and (ii) occurrence of severe (Grade 4) neutropenia. Occurrence will be displayed as the proportion of patients with an event for each study arm. Duration of severe (Grade 4) neutropenia in Cycle 1 will be analyzed with nonparametric analysis of covariance (ANCOVA) (Stokes 2012), while the occurrence of severe (Grade 4) neutropenia will be analyzed using modified Poisson regression (ie, Poisson regression with a robust error variance) (Zou 2004),. Unless otherwise specified, these endpoints will be evaluated for the induction treatment period, which is defined as the duration between the date of randomization and the end of the last cycle in the protocol-defined induction phase (ie, last cycle of placebo or trilaciclib plus E/P/A). There are multiple key secondary endpoints. To accommodate the primary and key secondary endpoints, a Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the multiple null hypotheses in the strong sense at a 1-sided α=0.025 level.

	These analyses will be conducted based on the ITT analysis set. The stratification factors of ECOG performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no) will be accounted for in the statistical analyses. Appropriate sensitivity analyses for the primary and key secondary endpoints will be conducted to evaluate the robustness of the results. Other secondary endpoints including antitumor activity as assessed by objective response and PFS (as assessed by RECIST version 1.1) and OS will be evaluated. Summaries of safety data will be performed using the safety analysis set. Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; Version 17.1 or later). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Absolute values and changes from baseline in vital signs, ECG results, and hematology and clinical chemistry parameters will be tabulated at each visit during the Treatment Phase. Toxicities for clinical labs will be characterized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. Shifts in toxicity grades from baseline will be summarized. Pharmacokinetic results will be analyzed and reported for the PK analysis set, separately for each analyte. Plasma concentration-time data will be tabulated descriptively and graphically by treatment group. Pharmacokinetic parameters will be calculated using noncompartmental methods based on the plasma concentration-time data. Pharmacokinetic parameters will be summarized descriptively.
Rationale for Number of Patients	The sample size calculation is based on demonstrating the superiority of trilaciclib + E/P/A versus placebo + E/P/A for the primary endpoints. To maintain the overall type I error rate using the most conservative Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.025/2 = 0.0125 is assigned to each outcome variable in the sample size calculation. Assuming a 95% evaluability rate, at least 106 patients need to be enrolled to complete the study.

4. INTRODUCTION

4.1. Background

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases worldwide and more than two-thirds of patients present with extensive-stage disease. Although response rates to first-line chemotherapy in extensive-stage SCLC are in the range of 50% to 60%, the median duration of response is short (approximately 4 months), with a median survival of 8 to 10 months and 2-year survival rates of less than 10% (Jemal 2009; Eckardt 2006; Noda 2002; Hanna 2006; Socinski 2009; Hermes 2008; Schmittel 2006; Lyman 2006). Increasing evidence suggests that immune responses against SCLC cells make immunotherapy a viable therapeutic approach in this disease (Horn 2016). Furthermore, there is evidence that certain chemotherapeutic regimens may augment the immunotherapeutic response in SCLC, in part by releasing neoantigens and educating the immune system against the surviving cancer cells.

Atezolizumab (Tecentriq®), is a monoclonal antibody that binds to programmed death-ligand 1 (PD-L1), inhibiting its interaction with the programmed cell death protein 1 (PD-1) receptor and releasing the PD-L1/PD-1 mediated inhibition of the immune response. Atezolizumab is an immunotherapy indicated for the treatment of locally advanced or metastatic urothelial carcinoma (UC) (approved in the United States in May 2016) and metastatic non-small cell lung cancer (NSCLC) (approved in the United States in October 2016). Etoposide and carboplatin (E/P) is a standard SCLC treatment and is currently under investigation with atezolizumab for the treatment of SCLC.

The major drawback to platinum-based chemotherapeutic regimens used in SCLC treatment is dose-limiting myelosuppression, which may antagonize the intended effects of the immunotherapy by reducing both the number and function of lymphocytes. Therefore, an approach to maintain immune system function while administering cytotoxic chemotherapy is needed to fully realize the therapeutic potential of immunotherapies.

Trilaciclib is a highly potent, selective, and reversible cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in development to preserve bone marrow and immune system function (including lymphoid progenitors and lymphocytes) from damage by chemotherapy, allowing faster hematopoietic recovery, preserving long-term bone marrow function, and enhancing the antitumor activity of chemotherapy. Trilaciclib is administered intravenously prior to every dose of chemotherapy in every cycle, eg, on Days 1 to 3 prior to E/P administration in 21-day cycles, for extensive-stage SCLC. This pulsatile dosing around chemotherapy administration allows preservation of the bone marrow and immune system without adding to the chemotherapy-induced myelosuppression caused by chronic inhibition of CDK4/6 in the bone marrow. Preserving adaptive immunity with trilaciclib may enhance the efficacy of chemotherapy combined with immune checkpoint inhibitors, supporting clinical testing of the novel combination of etoposide, carboplatin, and atezolizumab (E/P/A) therapy and trilaciclib.

4.2. Study Rationale

Nonclinical studies in mice have shown that trilaciclib causes a "priming" effect on bone marrow and immune cells. Specifically, trilaciclib administration causes a transient gap 1 (G1) cell cycle arrest in bone marrow progenitors and lymphocytes (B cells and thymocytes), thus protecting them from cytotoxic chemotherapy damage. The transient G1 cell cycle arrest is followed by a brief increased rate of proliferation up to 72 hours following trilaciclib administration before returning to a baseline proliferative rate within 1 week, as demonstrated by assessing 5-ethynyl-2'-deoxyuridine (EdU) incorporation in specific cell populations. In addition, trilaciclib can protect T lymphocyte numbers and functionality post chemotherapy treatment. In a well-established 5-fluorouracil (5-FU) treatment murine model, T lymphocyte populations recovered faster in mice that received up to 4 cycles of trilaciclib + 5-FU, compared to 5-FU alone. Splenocytes derived from mice that received trilaciclib + 5-FU and stimulated ex vivo with anti-cluster of differentiation 3 (CD3) and anti-CD28 antibodies demonstrated normal levels of interferon-gamma (IFNγ) and interleukin 2 (IL-2) release, while stimulated splenocytes from mice treated with 5-FU alone demonstrated a decreased release of both cytokines. Taken together, these data suggest that trilaciclib-mediated preservation of lymphocyte numbers and function, along with the transient increase in proliferation of lymphocytes and other immune cells coinciding with chemotherapy-associated neoantigen release, could allow for maximal priming of the immune system to generate an efficacious adaptive immune response.

Chemotherapy-induced lymphopenia is a well-known phenomenon, yet has not been well studied in the past. Chemotherapy-associated late bone marrow toxicity results from therapy-induced damage and premature exhaustion of hematopoietic stem cells (HSCs). Cytotoxics can cause direct damage to activated HSCs, but also induce functional attrition of HSCs indirectly through a process of proliferative exhaustion. This HSC intrinsic damage leads to a reduction of long-term multilineage reconstitution potential as well as myeloid-biased differentiation, resulting in lymphopenia. Nonclinical data demonstrate that trilaciclib administered prior to chemotherapy for multiple cycles can lead to a lasting protection of HSC function, thereby ameliorating the long-term toxicity associated with serial exposure to chemotherapy agents (ie, "exhaustion"), and preservation from myeloid-biased differentiation.

Chemotherapy-induced lymphopenia could potentially decrease the efficacy of immune checkpoint inhibitors when administered with chemotherapy. As a clinical biomarker of immune system function, baseline lymphocyte counts from patients with SCLC who received first-line E/P (N = 134) or second-line topotecan therapy (N = 78) were evaluated via a retrospective chart review and in data from 2 ongoing SCLC clinical trials testing the combination of trilaciclib with these chemotherapy regimens (first line, E/P, NCT02499770; and second line, topotecan, NCT02514447). Baseline lymphocyte counts from patients with SCLC were lower at the start of second-line treatment compared to the start of first-line treatment (1116 versus 1481/μL, respectively; $p = 0.0002$), demonstrating persistent lymphopenia months after first-line chemotherapy. In the ongoing trilaciclib SCLC studies, lymphocyte counts have remained relatively unchanged through repeated cycles of both first- and second-line chemotherapy, demonstrating preservation of this important cell population.

Currently, there are no approved treatments to decrease myelosuppression across multiple lineages by preserving hematopoietic stem and progenitor cell (HSPC) function. Although some therapies may help to address issues once they have occurred (eg, transfusions, growth factors, etc), there are no available options that provide patients with a means to effectively preserve HSPC and immune system function from chemotherapy-induced damage and the resultant negative impact. For this reason, patients receiving myelosuppressive chemotherapy often experience clinically significant consequences, such as severe neutropenia and risk of infections, anemia requiring red blood cell (RBC) transfusions, dose reductions, etc. Thus, myelosuppression continues to be a serious side effect of chemotherapy for patients with SCLC who have significant side effects from treatment, short time to progression, and poor overall survival (OS). This population would benefit from a therapeutic option that minimizes the myelosuppressive impact of treatment by reducing the frequency of severe cytopenias, preserving immune system function, and maintaining long-term bone marrow function. Minimizing myelosuppression should, ideally, lead to decreased chemotherapy-induced morbidity and mortality, facilitation of optimal standard of care chemotherapy regimens, and enhanced antitumor activity.

To evaluate the effect of trilaciclib in combination with chemotherapy and an immune checkpoint inhibitor, immunocompetent MC38 tumor-bearing mice were treated with trilaciclib, oxaliplatin, or anti-PD-L1 alone or in combination, and tumor size was measured during and post treatment for 100 days. The addition of trilaciclib to an oxaliplatin/anti-PD-L1 combination (TOP) treatment significantly improved the overall response rate, complete response rate, and median OS compared to oxaliplatin/anti-PD-L1 combination (93% vs 46%; 79% vs 38%; not reached at 100 days vs 59 days, respectively). Taken together, this demonstrates that trilaciclib, which has been shown to preserve immune function during chemotherapy, enhances the antitumor activity of chemotherapy/anti-PD-L1 combination therapy.

In summary, nonclinical data demonstrate that trilaciclib administration with chemotherapy preserves bone marrow and immune system function from damage by chemotherapy. Additionally, clinical data from Study G1T28-02 (Section 4.3.1), where patients received trilaciclib or placebo in combination with etoposide/carboplatin, provides compelling evidence that trilaciclib decreases myelosuppression across 3 lineages (neutrophils, RBC, and lymphocytes), and suggests that trilaciclib contributes to a more functional activated immune system as compared with placebo. It is this difference that is hypothesized to translate into potentially improved efficacy (eg, OS) when chemotherapy is combined with checkpoint inhibitors.

4.3. Summary of Clinical Data

4.3.1. Trilaciclib

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

Study G1T28-1-01 was a Phase 1a, safety, PK, and pharmacodynamic study of trilaciclib. Forty-five healthy male and female subjects were enrolled into 7 dose cohorts where trilaciclib was administered intravenous (IV) as a 30-minute infusion (randomized,

double-blind, placebo-controlled ascending doses of 6, 12, 24, 48, 96, or 192 mg/m^2, and an open-label expanded pharmacodynamic cohort at 192 mg/m^2).

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

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

Trilaciclib showed positive pharmacodynamic effects in 2 assays. Dose-dependent inhibition of ex vivo whole blood stimulation occurred following a single IV infusion of trilaciclib at 96 and 192 mg/m^2 (maximum mean inhibition of 37.2% and 60%, respectively, occurred 4 hours after the end of infusion). Lymphocyte proliferation started to recover 8 hours after the end of infusion, but inhibition of proliferation persisted until the last sampling time point of 24 hours. Assessment of bone marrow 24 hours after administration of trilaciclib at the biologically effective dose (BED) of 192 mg/m^2 revealed a significant decrease in the number of HSPCs in the synthesis (S)/gap 2 (G2)/mitosis (M) phases of the cell cycle (ie, an increase in the proportion of cells in G1 arrest). This G1 arrest persisted in the different progenitor lineages 32 hours after dosing. However, no changes were noted in the peripheral blood counts, indicating that the bone marrow arrest is transient and reversible and is consistent with the effects seen in animals.

Trilaciclib is also being tested in 2 ongoing Phase 1b/2a studies (G1T28-02 and G1T28-03). Study G1T28-02 is designed to assess the safety and PK of trilaciclib in combination with

E/P therapy for patients with newly diagnosed extensive-stage SCLC. Study G1T28-03 is designed to assess the safety and PK of trilaciclib in combination with topotecan for patients with previously treated extensive-stage SCLC. The safety profiles observed to date in G1T28-02 and G1T28-03 are consistent with the general safety profile of patients undergoing chemotherapy treatment; no new safety signals have been identified as of the trilaciclib IB data cutoff date of 20 May 2016.

In G1T28-02, a total of 19 patients were treated in the dose exploration Part 1, and 75 patients were treated in the placebo-controlled, double-blinded, randomized Part 2. (Please see the current version of the trilaciclib IB for detailed information on Part 1 patients.) The unblinded randomized results from Part 2 provide proof-of-concept evidence of the myelopreservation benefits of trilaciclib combined with E/P compared with placebo + E/P. The trilaciclib arm was favored across all neutrophil-related endpoints, including the proportion of patients with Grade 4 absolute neutrophil count (ANC) values (16/37 [43.2%] for placebo versus 2/38 [5.3%] for trilaciclib: p-value = 0.0001) and dose reductions due to neutropenia (10/37 [32.4%] for placebo versus 2/38 [5.3%] for trilaciclib: p-value = 0.0033). In alignment with the reduction of Grade 4 ANC events, the proportion of patients who received granulocyte colony-stimulating factor (G-CSF) was also significantly lower in the trilaciclib group (4/38 [10.5%]) than in the placebo group (24/37 [64.9%]: p-value < 0.0001). RBC endpoints also favored trilaciclib versus placebo, eg, 2/35 (5.7%) of patients enrolled on the trilaciclib arm received an RBC transfusion on/after Week 5 versus 8/37 (21.6%) of patients in the placebo arm. In addition, mean lymphocyte counts over time in the trilaciclib arm were greater than those observed in the placebo arm, and the recovery to baseline after each chemotherapy-induced lymphocyte nadir was faster in the trilaciclib arm compared with the placebo arm. Consistent with the faster recovery of lymphocyte counts, E/P + trilaciclib, as compared to E/P + placebo, not only increased the total number of circulating CD8+ cells during treatment, but also resulted in a larger population of activated CD8+ T cells, and fewer regulatory T cells; both of which are consistent with a more robust immune response which could correlate with improved antitumor responses. In Part 2, almost all patients reported at least 1 TEAE, and almost all patients reported TEAEs related to etoposide or carboplatin. Approximately half the patients reported TEAEs related to trilaciclib, but none were ≥ Grade 3, which suggests that trilaciclib is not associated with severe toxicity. There were notably fewer high-grade (≥ Grade 3 and ≥ Grade 4) TEAEs reported during treatment with trilaciclib compared with placebo, an observation primarily driven by a significant decrease in the number of hematologic high-grade TEAEs reported in the trilaciclib arm. Fatigue, nausea, thrombocytopenia, and anemia were the most frequent TEAEs in the trilaciclib group. Neutropenia, anemia, alopecia, and thrombocytopenia were the most frequent TEAEs in the placebo group.

In G1T28-03, the majority of patients (92.9%; 13 of 14) reported TEAEs, with the most common (ie, reported by > 50% of patients) being thrombocytopenia, neutropenia, anemia, and leukopenia. TEAEs considered related to trilaciclib per investigator assessment were reported by 4 patients (28.6%). The majority of patients (85.7%) reported at least 1 Grade 3, 4, or 5 TEAE; those reported by more than 1 patient included thrombocytopenia, leukopenia, neutropenia, anemia, neutrophil count decreased, pneumonia, and dyspnea. The majority of the Grade 3, 4, or 5 TEAEs have been reported by patients in Cohorts 1 and 2, likely due to the supratherapeutic levels of topotecan observed in these patients, which may be responsible for the higher number of hematology-related TEAEs in Cohorts 1 and 2. Over one-half of

patients (64.3%) reported an SAE, all of which were considered unlikely or not related to trilaciclib and did not meet DLT criteria. One patient died during participation in the study due to an SAE of disease progression that was considered unrelated to trilaciclib by the investigator.

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

4.3.2. Atezolizumab

Atezolizumab (Tecentriq®) has been evaluated in several clinical indications. At this time, atezolizumab is approved for patients with UC and NSCLC, for which safety data is available and briefly summarized below. Further details are provided in the Atezolizumab Guidance for the Investigator (Appendix 1) and atezolizumab prescribing information (Appendix 2).

Adverse Reactions

The most common adverse reactions (rate ≥ 20%) in patients with UC included fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%).

The most common adverse reactions (rate ≥ 20%) in patients with NSCLC included fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%).

Serious Adverse Reactions

Based on pooled data from atezolizumab single-agent studies in patients with UC, NSCLC, and other indications (N = 1978), with additional safety data as of 10 May 2016 across patients who have received atezolizumab single agent or in combination with chemotherapy/targeted therapy (N = 6053) (where applicable), the serious adverse drug reactions (ADRs) occurring in > 1% of patients included the following: dyspnea (3.0%, 60 of 1978 patients), pyrexia (2.4%, 48 of 1978 patients), back pain (1.2%, 23 of 1978 patients), pneumonitis (fatal outcome expected for reporting purposes) (1.2%, 24 of 6053 patients), and abdominal pain (1.1%, 22 of 1978 patients).

Potential risks and adverse events of special interest (AESI) identified for atezolizumab are described in Section 4.4.4.2, and full details can be found in the Atezolizumab Guidance for the Investigator (Appendix 1), atezolizumab prescribing information (Appendix 2), and atezolizumab AESI list (Appendix 3).

4.4. Summary of Nonclinical Data

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

Nonclinical data related to atezolizumab is provided in the prescribing information (Appendix 2).

4.4.1. Pharmacology Studies

Trilaciclib

Through a structure-based design approach to optimize potency, selectivity, and drug metabolism and PK properties, G1 Therapeutics, Inc. identified trilaciclib as a highly potent inhibitor of CDK4 and CDK6 (half maximal inhibitory concentration [IC_{50}] values of 0.8 and 6 nM, respectively) that is highly selective for CDK4 versus cyclin-dependent kinase 2 (CDK2) (> 2000-fold selectivity).

The trilaciclib-induced G1 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 coadministration of trilaciclib with myelosuppressive chemotherapy leads to improved CBC recovery of all blood lineages and increased survival. In addition, administration of trilaciclib with every cycle of the highly myelosuppressive chemotherapy 5-FU for a total of 4 cycles demonstrated that the reduction in chemotherapy-induced myelosuppression persisted following Cycle 4. While the extent and duration of nadir in CBCs worsened after each cycle of 5-FU administered alone, coadministration of trilaciclib with 5-FU ameliorated this worsening effect and the animals that received trilaciclib + 5-FU demonstrated a faster rate of recovery of CBCs compared with the 5-FU alone group following Cycle 4. In accordance with the single-dose study, trilaciclib administration with all cycles of 5-FU maintained the protective effect against 5-FU-induced DNA damage in HSPCs over multiple cycles, leading to an effect that persisted and was greater following multiple cycles of trilaciclib + 5-FU compared with 5-FU alone. In addition, bone marrow obtained from mice that received 4 cycles of trilaciclib administered prior to every dose of 5-FU was more robust at hematopoietic reconstitution of lethally irradiated mice following bone marrow transplantation compared with bone marrow obtained from mice that received 4 cycles of 5-FU alone, suggesting that trilaciclib administered with chemotherapy can preserve stem cell function.

Retinoblastoma (Rb) is the direct downstream target of CDK4/6 and its expression is required for CDK4/6-dependent cells. Importantly, cancers that delete Rb do not require CDK4/6 activity for cell cycle progression (Fry 2004); therefore, loss of Rb is a hallmark identifier of CDK4/6 independence. Since inactivation of the retinoblastoma gene (RB-1) is an obligate event in SCLC development (D'Amico 1992; Heighway 2004; Yuan 1999; Cagle 1997; Gouyer 1994, Peifer 2012; Rudin 2012), this tumor type is highly resistant to CDK4/6 inhibitors and coadministration of CDK4/6 inhibitors with DNA damaging chemotherapeutic agents such as those used in SCLC are not expected to antagonize the efficacy of such agents. In vitro analysis has shown that RB-1 inactive cells are resistant to CDK4/6 inhibition and therefore are not protected from chemotherapy when cotreated with trilaciclib. To expand these findings in vivo, trilaciclib was tested alone and in combination with topotecan or an E/P combination regimen in a cell-based xenograft SCLC model (H69) in immune-deficient mice. Trilaciclib administered alone or 30 minutes before E/P or topotecan was well tolerated, with no additive weight loss or toxicity. Single agent trilaciclib was inactive towards NCI-H69 SCLC tumors and combination with an E/P regimen did not

result in additive efficacy, nor did it antagonize the intended effects of E/P. Combination of trilaciclib and topotecan was superior to topotecan alone during dosing and the addition of trilaciclib extended the statistically significant ($p < 0.05$) antitumor effect of topotecan after dosing. Thus, trilaciclib was well tolerated and did not antagonize the effects of chemotherapy in a CDK4/6-independent (RB-1 inactive) SCLC tumor model.

Atezolizumab

A summary of the pharmacology studies of atezolizumab is provided in the prescribing information (Appendix 2).

4.4.2. Pharmacokinetic Studies

Trilaciclib

Pharmacokinetic (PK) studies in rats and dogs showed that the relationship between dose level and plasma exposure to trilaciclib was generally similar between males and females and did not change with repeated daily dosing. Exposure to trilaciclib increased with dose level, but not always proportionally. Plasma half-life values for trilaciclib after IV administration were approximately 4 hours in rats and dogs.

In vitro analyses of direct and time-dependent inhibition suggest that drug interactions based on inhibition of cytochrome P40 (CYP)1A2-, 2B6-, 2C8-, 2C9-, 2C19-, and 2D6-mediated metabolic pathways are unlikely at concentrations of trilaciclib below 100 µM (44,600 ng/ml). Drug interactions based on trilaciclib mechanism-based inhibition of CYP3A4-mediated metabolic pathways are possible. 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.

While etoposide is a CYP3A4 substrate, there are no specific label warnings regarding coadministration with CYP3A4 inhibitors. This may in part be due to the relatively equal contributions of renal and hepatic clearance to the total clearance of etoposide. In addition, administration of oral ketoconazole, a potent CYP3A4 and uridine disphosphate glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) inhibitor, with oral etoposide for 3 of every 5-week cycles resulted in an increase of the median AUC of oral etoposide of only 20% and did not alter its toxicity profile (Yong 2007). In the present Study G1T28-05, IV trilaciclib will be administered prior to IV etoposide on Days 1 to 3 of 21-day cycles in patients with adequate renal function. In the Phase 1b dose-finding portion of Part 1 of the G1T28-02 study in patients with newly diagnosed SCLC, where the same doses of etoposide of carboplatin were used as in this study, PK of etoposide, carboplatin, and trilaciclib were assessed on Days 1 and 3 of the first cycle. The PK of etoposide and carboplatin was consistent with historical data, indicating the lack of a drug-drug interaction between trilaciclib and etoposide or carboplatin.

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)-, organic cation transporter 1 (OCT1)-, or organic anion transporting polypeptide 1B3 (OATP1B3)-mediated transport. Trilaciclib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1), multidrug and toxin extrusion 2-K (MATE2-K), and organic cation transporter 2 (OCT2) (IC_{50} values were 0.175, 0.071, and 0.152 μM, respectively), and therefore, may be a cause of a DDI if coadministered with substrates of these transporters.

Carboplatin has been reported (Yonezawa 2006) to not be a substrate for OCT2, MATE1, or MATE2. Etoposide has not been reported to be a substrate for any of these 3 transporters, and by structure is not expected to be a substrate. Based upon these data, a clinically significant alteration of carboplatin or etoposide PK due to trilaciclib inhibition of OCT2, MATE1, or MATE2-K is not expected, and none was detected in the G1T28-02 study in patients with newly diagnosed SCLC.

Atezolizumab

A summary of the PK studies of atezolizumab is provided in the prescribing information (Appendix 2).

4.4.3. Toxicity and Safety Studies

Trilaciclib

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

For further information, please refer to the trilaciclib IB.

Atezolizumab

A summary of the toxicity and safety studies of atezolizumab is provided in the Guidance to the Investigator (Appendix 1) and prescribing information (Appendix 2).

4.4.4. Potential Risks

4.4.4.1. Trilaciclib

When administered IV daily for 7 days, trilaciclib was tolerated in rats at up to 50 mg/kg (approximately 300 mg/m^2) and in dogs at up to 15 mg/kg (approximately 300 mg/m^2), with toxicity characterized chiefly by reduced hematopoiesis that involved all cell lineages and was a reflection of the drug's intended pharmacodynamic activity. The magnitude and/or duration of effect differed among cell lineages, but were dose related in all lineages. Effects on hematopoiesis were readily monitored by peripheral blood cell counts and were reversible when dosing stopped. Clinically significant leukopenia occurred in rats and dogs given IV

trilaciclib for 7 days at ≥ 150 and 300 mg/m^2, respectively, and it led to morbidity and mortality in dogs given daily doses for 6 days at 900 mg/m^2.

In addition to the intended effects on hematopoiesis, animal studies with trilaciclib suggest that potential side effects in human patients might include the following:

- Pulmonary macrophage accumulation: In rats, daily oral doses of trilaciclib for 14 days at ≥ 5 mg/kg (≥ 30 mg/m^2) resulted in minimal to mild accumulation of foamy macrophages in alveoli. The magnitude of this finding increased with dose level, but it was not associated with any discernable change in the rate or character of respiration. Macrophage accumulation showed evidence of resolving within 3 weeks after dosing stopped. Pulmonary macrophage accumulation was also seen in dogs given daily IV doses of trilaciclib by 30-minute infusion at 45 mg/kg (900 mg/m^2) for 5 days, at which point dosing was stopped due to toxicity. The DLT in these dogs was considered to be severe immunocompromise secondary to inhibition of myelopoiesis and lymphopoiesis; ie, an extension of the primary pharmacodynamic activity of trilaciclib.
- Increased heart rate: In dogs, single IV doses of trilaciclib at ≥ 15 mg/kg (≥ 300 mg/m^2) produced increases in heart rate that were relatively mild (30 to 60 beats per minute [bpm]) and resolved within a few hours.
- Effects on liver: Daily IV doses of trilaciclib in rats at ≥ 10 mg/kg/day (≥ 60 mg/m^2/day) and in dogs at ≥ 15 mg/kg/day (approximately 300 mg/m^2/day) resulted in slightly increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels. Liver-related effects in both species were reversible within 2 weeks after the last dose. There were no effects on liver in rats given daily oral doses for 14 days at up to 30 mg/kg (180 mg/m^2).
- Local irritation at the infusion site: Dogs given daily doses of trilaciclib for 7 days had occasional episodes of swelling/edema at the infusion site. This was considered likely to be due to leakage or accidental injection of dosing solution into the perivenous tissue.

The profile of TEAEs reported in the trilaciclib clinical development program are consistent with the underlying patient population with SCLC undergoing chemotherapy. There are no consistent patterns of TEAEs that can be considered attributable to trilaciclib. In addition, there have been no new risks identified and the preclinical risks have not been linked to clinical observations.

4.4.4.2. Atezolizumab

Per Section 5, Warnings and Precautions in the prescribing information for atezolizumab (Appendix 2), the **important identified** risks for atezolizumab are described in Table 4-1. A summary of potential risks for atezolizumab is provided in the Atezolizumab Guidance for the Investigator (Section 1.4, Appendix 1), the prescribing information (Appendix 2), and in Table 4-2. A list of AESI identified for atezolizumab is provided in Appendix 3. Please refer to the Atezolizumab Guidance for the Investigator (Appendix 1) and the full atezolizumab prescribing information (Appendix 2) for important dose management information specific to adverse reactions.

Table 4-1 Important Identified Risks for Atezolizumab

Identified Risk	Description of Risk
Immune-related pneumonitis	Pneumonitis occurred in 3.1% (68/2160) of patients who received atezolizumab. The majority of patients experienced only mild to moderate events. Of the 68 patients, 64% (36/56) of the All NSCLC group and 75% (9/12) of the All UC group experienced events with a maximum severity of Grade 1 or 2. One event was fatal in the All NSCLC group (considered unrelated to atezolizumab), and no events were fatal in the All UC group. The median time to onset was 3.5 months (range: 3 days to 20.5 months). The median duration was 1.5 months (range: 0 days to 15.1 + months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 10 (0.5%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (34/2160) of patients receiving atezolizumab. As expected, pneumonitis events occurred more frequently in the NSCLC patient population, most likely due to higher baseline incidence, higher prevalence of other risk factors, and atezolizumab-induced immunologic response to the tumor.
Immune-related hepatitis	Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with atezolizumab. Most of the hepatic events identified were non-serious elevations of liver enzymes. Hepatitis occurred in 0.3% (7/2160) of patients who received atezolizumab. The median time to onset was 1.1 months (range: 9 days to 7.9 months). The median duration was 1 month (range: 9 days to 1.9+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 2 (< 0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (5/2160) of patients receiving atezolizumab. All of these events resolved with the exception of 1 case of Grade 1 hepatitis, which was resolving at the time of data cutoff. Additionally, 1 patient (< 0.1%) experienced hepatic failure (with fatal outcome, considered unrelated to study therapy).
Immune-related colitis	Cases of diarrhea or colitis have been observed in clinical trials with atezolizumab. Colitis occurred in 1.1% (23/2160) of patients who received atezolizumab. The median time to onset was 4 months (range: 15 days to 15.2 months). The median duration was 1.4 months (range: 3 days to 17.8+ months; + denotes a censored value). Colitis led to the discontinuation of atezolizumab in 5 (0.2%) patients. Colitis requiring the use of corticosteroids occurred in 0.5% (10/2160) of patients receiving atezolizumab.
Immune-related pancreatitis	Pancreatitis and elevations in serum amylase and lipase occurred in 0.5% (10/2160) of patients who received atezolizumab. Most events identified were non-serious elevations in lipase or amylase. A total of 4 (0.2%) patients experienced pancreatitis, including 1 patient with acute pancreatitis. The median time to onset was 5.5 months (range: 9 days to 16.9 months). The median duration was 19 days (range: 3 days to 11.2+ months; + denotes a censored value). Pancreatitis requiring the use of corticosteroids occurred in < 0.1% (2/2160) of patients receiving atezolizumab.

Identified Risk	Description of Risk
Immune-related diabetes mellitus	Diabetes mellitus occurred in 0.3% (7/2160) of patients who received atezolizumab (4 reports of diabetes mellitus, 2 reports of type 1 diabetes mellitus and 1 report of type 2 diabetes mellitus). Of these 7 patients, 2 developed serious events and 5 developed events that were considered non-serious. Two cases resolved, 1 case resolved with sequelae, and 4 were not resolved by the time of the clinical cutoff. The time to onset ranged from 3 days to 6.5 months. Diabetes mellitus led to the discontinuation of atezolizumab in 1 (< 0.1%) patient.
Immune-related hypothyroidism	Hypothyroidism occurred in 4.7% (101/2160) of patients who received atezolizumab. The median time to onset was 5.5 months (range: 15 days to 31.3 months). Events have generally been mild, and patients who received treatment with thyroid replacement were able to continue on study treatment. A total of 19 patients experienced adverse events that appear in both the hypothyroidism and hyperthyroidism standardised MedDRA queries (SMQs). These 19 patients are therefore duplicated in the data presented on hypothyroidism and hyperthyroidism. The vast majority of the duplicated patients were reported to have experienced blood thyroid stimulating hormone increased. Because primary hypothyroidism is more prevalent than hyperthyroidism in patients treated with both atezolizumab and other drugs in this class, it is probable that the majority of patients that appear in both searches actually developed hypothyroidism.
Immune-related hyperthyroidism	Hyperthyroidism occurred in 1.7% (36/2160) of patients who received atezolizumab. The median time to onset was 3.5 months (range: 21 days to 31.3 months). No severe events were identified. Please see immune-related hypothyroidism above for patients duplicated in the data presented on hypothyroidism and hyperthyroidism.
Immune-related adrenal insufficiency	Adrenal insufficiency occurred in 0.3% (7/2160) of patients who received atezolizumab. The median time to onset was 5.7 months (range: 3 days to 19 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (6/2160) of patients receiving atezolizumab.
Immune-related hypophysitis	Hypophysitis occurred in < 0.1% (1/2160) of patients who received atezolizumab. The time to onset for this patient was 13.7 months.
Immune-related Guillain-Barré syndrome	Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.2% (5/2160) of patients who received atezolizumab. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 4.6 months (0+ day to 8.3+ months). Guillain-Barré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (2/2160) of patients receiving atezolizumab
Immune-related myasthenic syndrome/myasthenia gravis	Myasthenic syndrome/myasthenia gravis, which may be life threatening, were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy. Four cases of myasthenia gravis or myasthenic

Identified Risk	Description of Risk
	syndrome have been reported from across the entire development program as of 07 July 2016. The first case concerned a 64-year-old male patient receiving atezolizumab monotherapy for renal cell carcinoma (RCC) in the Study PCD4989g (GO27831). The patient was positive for acetylcholine receptor binding antibodies and acetylcholine receptor modulating antibodies. The event was considered serious, and the patient was treated with corticosteroids and discontinued from the study. A second case of myasthenia gravis was received concerning a 64-year-old male patient receiving atezolizumab in combination with ipilimumab in Study GO29322. The event was considered serious, and the patient was treated with corticosteroids and mycophenolate and discontinued from the study. The third case concerned a 56-year-old male who developed bilateral ptosis while receiving atezolizumab monotherapy for urothelial bladder cancer in the expanded access program ML29725. The patient was positive for acetylcholine receptor antibodies, acetylcholine receptor modulating antibodies and striated muscles antibodies and was diagnosed with myasthenia gravis. The event was considered serious and the patient was treated with corticosteroids and discontinued from atezolizumab. The fourth case concerned a 67-year-old female patient receiving atezolizumab in combination with cobimetinib in Study GP28363. The patient developed ptosis, an acetylcholine receptor antibody test was negative and the results of the nerve conduction studies were normal. The patient was diagnosed with myasthenia gravis and treated with pyridostigmine, and atezolizumab and cobimetinib were discontinued.
Immune-related meningoencephalitis	Meningitis occurred in 0.1% (3/2160) of patients who received atezolizumab. The time to onset ranged from 15 to 16 days. All 3 patients required the use of corticosteroids and discontinued atezolizumab. Encephalitis occurred in < 0.1% (2/2160) of patients. The time to onset was 14 and 16 days. Encephalitis led to discontinuation of atezolizumab in 1 (< 0.1%) patient. Encephalitis requiring the use of corticosteroids occurred in < 0.1% (1/2160) of patients receiving atezolizumab
Immune-related myocarditis	Although no cases were identified from the pooled 2160 patients who received single agent atezolizumab, 2 cases of myocarditis, including a life-threatening case, have been reported from across the entire development program as of 20 February 2017. The time to onset ranged from 18 to 33 days. The first case concerned a 59-year-old female patient with follicular lymphoma receiving atezolizumab in combination with bendamustine and obinutuzumab in Study BO29563. Her cardiac biopsy revealed T-cell infiltration. The second case concerned a 69-year-old male patient with RCC receiving atezolizumab in combination with bevacizumab in Study WO29637. He developed clinical sign/symptoms including chest pressure, and positive diagnostic test results including abnormal electrocardiogram (ECG) and increased cardiac enzymes. Both patients discontinued atezolizumab and required the use of corticosteroids

Identified Risk	Description of Risk
Immune-related nephritis	Immune-related nephritis is a relatively rare complication of checkpoint inhibitor therapy with the most common reported underlying pathology being acute tubulo-interstitial nephritis (ATIN). The most common presentation is an asymptomatic increase in creatinine levels. In the absence of alternative etiologies (eg, prerenal and postrenal causes, and concomitant medications), immune-related nephritis is defined as renal dysfunction requiring steroids treatment and/or confirmed by biopsy
Infusion-related reactions	Infusion-related reactions are known to occur with the administration of monoclonal antibodies. The signs and symptoms of infusion-related reactions share considerable overlap with several very common atezolizumab adverse drug reactions (ADRs) including influenza-like illness, pyrexia, and rash. The identified reactions occurred within 24 hours of atezolizumab administration and were generally mild to moderate in severity, and only 10 patients (0.5%) out of the 2160 pooled UC and NSCLC patients developed SAEs. Twenty-four (1.1%) of 2160 patients were reported to have experienced the event of infusion reaction (with 2 serious events). Across all 2160 patients, 16 patients (0.7%) were reported to have hypersensitivity (with 4 serious events), and none were reported to have experienced anaphylactic or anaphylactoid reactions.

Notes: The cutoff dates for the following studies are 31 March 2016 for Study PCD4989g, 07 January 2015 for FIR, 01 December 2015 for POPLAR, 01 December 2015 for BIRCH, 07 July 2016 for OAK, and 04 July 2016 for IMvigor 210.

Table 4-2 Potential Risks for Atezolizumab

Potential Risk	Description of Risk
Anti-drug antibodies (ADA)	**Cynomolgus Monkey Studies**: After a single intravenous (IV) administration of atezolizumab to cynomolgus monkeys, antidrug antibodies (ADAs) were detected in 12 of 12 animals (100%) at Day 14; 11 of 12 animals remained ADA positive after Day 14 until the end of the study. Fifty of 56 animals (89%) given atezolizumab tested positive for ADA following 9 weekly doses. While ADAs affected the pharmacokinetics of some animals, average exposure for ADA -positive and ADA-negative animals was similar. **Clinical Studies**: ADAs have been observed in the clinical trials to date for atezolizumab; however, at doses of 10 mg/kg and above, they do not appear to affect exposure. The incidence of serious adverse events (SAEs) was increased in ADA-positive patients (40.5%) compared with ADA-negative patients (34%), but no specific trend in either MedDRA system organ class (SOC) or individual adverse event preferred term (PT) was identified in ADA-positive patients. In all safety-evaluable patients with available post-treatment ADA status (n = 2007), the incidence of hypersensitivity events and infusion-related reactions was low and numerically higher in ADA- positive than ADA-negative patients. Hypersensitivity events were reported in 24 patients (1.2%):

Potential Risk	Description of Risk
	9 ADA-negative (0.7%) and 15 ADA- positive (1.9%) patients. Infusion-related reactions occurred in 25 patients (1.2%): 14 ADA-negative (1.1%) and 11 ADA-positive (1.4%) patients. The incidences of all grade AEs, Grade 5 AEs, AEs leading to treatment discontinuation, AEs leading to dose interruption, and adverse events of special interest (AESIs) were similar irrespective of post-baseline ADA status (negative or positive). Numerical differences were observed in Grade 3/4 AEs (40.7% in ADA-negative vs. 47.0% in ADA-positive patients), but no individual PT could be identified to explain this difference.
Embryofetal toxicity	Several nonclinical studies have demonstrated that the PD-L1/ PD-1 signaling pathway is critical in establishing and maintaining maternal/fetal tolerance, which is essential for embryo-fetal survival during gestation (Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011). Inhibition of the PD-L1/PD-1 pathway has not been reported to result in teratogenic effects, and syngeneic homozygous knockout fetuses (PD-L1 or PD-1 knockouts) develop normally and have not shown skeletal or visceral defects. Administration of atezolizumab is expected to have an adverse effect on pregnancy via modulation of maternal/fetal tolerance, and poses a risk to the human fetus, including embryo-lethality via an increased risk of immune- mediated rejection. No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. There are no clinical studies of atezolizumab in pregnant women. Atezolizumab is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.
Immune-related myositis	Immune-related myositis occurred in 0.2% (4/2160) of metastatic urothelial carcinoma (mUC) and NSCLC patients who received single-agent atezolizumab. Patients may experience weakness, tenderness and aching of the muscles. Four cases containing 7 events were identified, including 3 cases of polymyalgia rheumatica from studies IMvigor 210, FIR and OAK, and 1 case of dermatomyositis from BIRCH. Atezolizumab treatment was not changed for all polymyalgia rheumatica events and was interrupted for the dermatomyositis events. The dermatomyositis events had features consistent with cancer associated myositis, and there was insufficient evidence to support the attribution of a causal relationship between myositis and atezolizumab. Myositis is an ADR for other immune checkpoint inhibitors. Myositis remains a potential risk for atezolizumab and will continue to be monitored by routine pharmacovigilance
Immune-related ocular inflammatory toxicity	Ocular inflammatory toxicity events occurred in 0.5% (10/2160) of mUC and NSCLC patients who received single-agent atezolizumab. Most of the ocular events identified were nonserious, with Grade 1 or 2 in severity. Four events were considered relate to atezolizumab and led to treatment discontinuation, including 1 serious retinopathy, 1 serious optic neuritis, 1 nonserious optic neuritis, all from Study OAK, and 1 nonserious episcleritis from Study BIRCH. However, these cases either had clear alternate explanations, including cataract

Potential Risk	Description of Risk
	surgery prior to event, lung cancer paraneoplastic related neuropathy, previous brain radiotherapy or had very limited information reported for assessment. Two cases of uveitis, from Study FIR and OAK, were both considered not related to study treatment. Based on the totality of the data to date, the evidence does not support a definitive causal association between Atezolizumab and ocular inflammatory toxicity. Based on the totality of the data to date, the evidence does not support a definitive causal association between atezolizumab and ocular inflammatory toxicity. The etiology of uveitis or optic neuritis may include autoimmunity, demyelinating disorders, inflammation, infections, drug or toxic reasons, trauma, or the underlying malignancy (Guly and Forrester 2010, Kale 2016). Immune-related ocular inflammatory toxicity is considered an important risk for atezolizumab, and it will continue to be monitored by routine pharmacovigilance.
Immune-related severe cutaneous reactions	Severe cutaneous adverse reactions occurred in 0.6% (13/2160) of mUC and NSCLC patients who received single-agent atezolizumab. Most of the cutaneous events identified were nonserious; however, 1 patient (< 0.1%) experienced a serious case of bullous dermatitis from Study OAK that resolved following treatment with corticosteroids. Across the clinical development program, isolated severe skin toxicities including lichenoid drug reaction, pemphigoid, Stevens-Johnson syndrome (localized to the eye) and toxic epidermal necrolysis have been reported; however, causality to atezolizumab could not be confirmed. Severe cutaneous adverse reactions have been observed in patients treated with other immune checkpoint inhibitors and are an important potential risk for atezolizumab. It will continue to be monitored by routine pharmacovigilance.
Immune-related vasculitis	Nonclinical studies demonstrated dose-dependent evidence of arteritis/periarteritis in cynomolgus monkeys treated with atezolizumab. Vasculitis occurred in 0.2% (5/2160) of mUC and NSCLC patients who received single-agent atezolizumab. One serious event of Henoch-Schonlein purpura nephritis was reported that is also represented in the information for immune-related nephritis due to the overlap in PTs in the search strategies. Three cases of polymyalgia rheumatica from studies IMvigor 210, FIR and OAK were reported and are described in the information for immune-related myositis, due to similar overlapped terms in the search strategies. One case of nonserious injection site vasculitis was reported from Study BIRCH. Currently, no causal relationship with atezolizumab has been established. Immune-related vasculitis is considered an important potential risk of atezolizumab and it will continue to be monitored by routine pharmacovigilance

Potential Risk	Description of Risk
Autoimmune hemolytic anemia	Autoimmune hemolytic anemia event is a rare condition and a known ADR for products similar in class (rare to uncommon 0.1% to ≤ 1%). An analysis was done of the Roche global safety database with a cut-off date 05 January 2017, which identified 5 patients with evidence of autoimmune hemolytic anemia reported in atezolizumab-treated patients. All cases had possible alternate etiologies including concomitant medications, suspected infection, and concurrent therapy with an additional immunomodulating agent. Autoimmune hemolytic anemia is considered an important potential risk of atezolizumab and it will continue to be monitored by routine pharmacovigilance.

Clinical cutoff dates: GO27831: 31 March 2016, GO28625: 07 January 2015, GO28753: 01 December 2015, GO28754: 01 December 2015, GO29293: 04 July 2016, GO28915: 07 July 2016.

ADA status cutoff dates: GO27831: 02 December 2014, GO28625: 07 January 2015, GO28753: 08 May 2015, GO28754: 28 May 2015, GO29293: 04 July 2016, GO28915: 07 July 2016

Other AESI that are being monitored for atezolizumab include immune-related myositis, immune-related nephritis, immune-related uveitis, immune-related myopathies, and rhabdomyolysis. A list of AESI identified for atezolizumab is provided in Appendix 3.

Other safety events of interest that are currently being monitored in the atezolizumab clinical program include the following: immune-related myopathies, including rhabdomyolysis. Reports of myopathies, including rhabdomyolysis, have been observed across the clinical development program of atezolizumab. Patients who present with signs or symptoms of muscular pain should be assessed for inflammatory causes of muscle pain. Management of these patients should be along institutional guidelines.

4.5. Study and Dose Rationale

In a Phase 1a, safety, PK, and pharmacodynamic study of trilaciclib (Study G1T28-1-01), 45 healthy male and female subjects were enrolled into 7 dose cohorts where trilaciclib was administered IV as a 30-minute infusion (randomized, double-blind, placebo-controlled ascending doses of 6, 12, 24, 48, 96, or 192 mg/m^2, and an open-label expanded pharmacodynamic cohort at 192 mg/m^2). Trilaciclib was well tolerated, with no DLTs or SAEs reported. Pharmacodynamic analysis 24 hours following administration of trilaciclib 192 mg/m^2 demonstrated a significant decrease in the number of bone marrow HSPCs in the S/G2/M phases of the cell cycle (ie, an increase in the proportion of cells in G1 arrest), which persisted to 32 hours. Thus, dosing of trilaciclib 200 mg/m^2 (rounded up from the BED of 192 mg/m^2) was selected as the starting dose for the subsequent Phase 1b/2a SCLC studies (G1T28-02 [administered prior to etoposide and carboplatin] and G1T28-03 [administered prior to topotecan]). Based on the Phase 1b results from these 2 studies, trilaciclib 240 mg/m^2 was chosen as the recommended Phase 2 dose. In the G1T28-02 study, there was no impact of trilaciclib on etoposide or carboplatin PK. Based on the PK and safety from the G1T28-02 study, the lack of predicted drug-drug interactions and nonoverlapping toxicities between atezolizumab and trilaciclib, etoposide, and carboplatin, the evaluation of this 4-drug combination is reasonable. The goals of the present study are to assess the safety, tolerability, and efficacy of combining trilaciclib 240 mg/m^2 with E/P/A therapy.

4.6. Risk/Benefit Assessment

Trilaciclib is being developed to reduce chemotherapy-induced myelosuppression, which is a significant issue. Nonclinical data demonstrate that trilaciclib administration with chemotherapy preserves bone marrow and immune system function from damage by chemotherapy. In addition, preliminary clinical data suggest that lymphocyte numbers are relatively unchanged when trilaciclib is used in combination with chemotherapy. Preserving adaptive immunity with trilaciclib may enhance the efficacy of chemotherapy combined with immune checkpoint inhibitors, supporting clinical testing of the novel combination of E/P/A therapy and trilaciclib.

Given the paucity of hematologic toxicities associated with atezolizumab (Section 6.1 of the atezolizumab package insert), the addition of atezolizumab to E/P chemotherapy is not predicted to influence the underlying myelosuppression profile of E/P. Multiple studies of chemotherapy administered in combination with checkpoint inhibitors suggest that the addition of a checkpoint inhibitor to a myelosuppressive chemotherapy backbone, does not result in any new safety signals and does not result in a clinically relevant exacerbation of the chemotherapy-induced myelosuppression (Ghandi 2018; Langer 2016; Rizvi 2016; Jotte 2018). Therefore, the potential myelopreservation benefit from the addition of trilaciclib to E/P can be evaluated in a setting that also includes atezolizumab.

Bone marrow HSPCs require CDK4/6 for proliferation. SCLC tumors are almost universally CDK4/6 independent by virtue of various genetic mutations in the RB-1 gene that result in the loss of the Rb protein, which is the downstream target of CDK4/6. Therefore, the risk of producing a G1 cell cycle arrest of the tumor cells, and thereby protecting the tumor from chemotherapy, is small. As stated in Section 4.5, the BED of IV trilaciclib is 192 mg/m^2 and a dose of 200 mg/m^2 was used as the initial starting dose for administration on Days 1 to 3 of every 21-day cycle in the G1T28-02 study. However, based on clinical data from G1T28-02 and G1T28-03, the recommended Phase 2 dose of trilaciclib is 240 mg/m^2. Therefore, trilaciclib 240 mg/m^2 administered on Days 1 to 3 of every 21-day cycle of E/P/A therapy will be used in the present study.

In conclusion, the possible benefits of combining trilaciclib at a dose of 240 mg/m^2 with E/P/A therapy to preserve bone marrow and immune system function from damage by chemotherapy and potentially increase the activity of the E/P/A combination regimen outweigh the potential risks.

5. STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, and [redacted] and endpoints of this study are presented in Table 5-1. Please note that the key secondary endpoints are described based on geographic region, consistent with the advice received from regulatory authorities in the respective regions, and with reference to ICH E17: General Principles for Planning and Design of Multiregional Clinical Trials.

Table 5-1 G1T28-05: Study Objectives and Endpoints

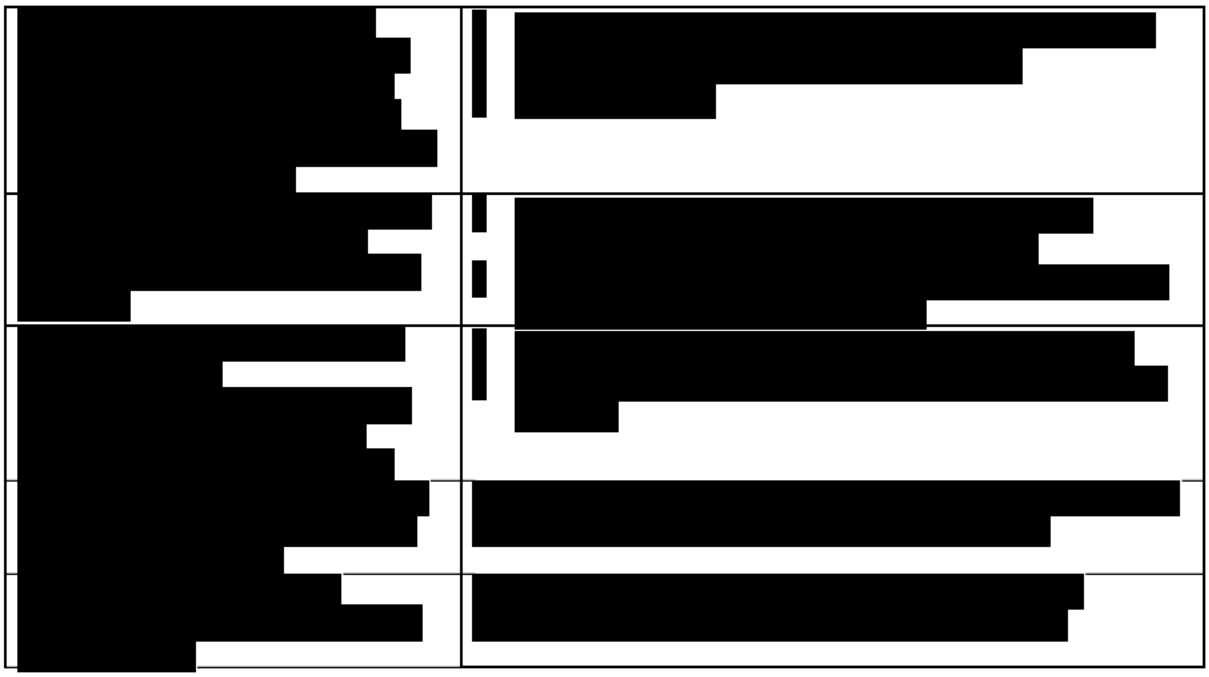
PRIMARY OBJECTIVES	**PRIMARY ENDPOINTS**	
Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression in patients with SCLC undergoing treatment with E/P/A	**All Regions** • Duration of severe (Grade 4) neutropenia in Cycle 1 • Occurrence of severe (Grade 4) neutropenia	
KEY SECONDARY OBJECTIVES	**KEY SECONDARY ENDPOINTS**	

Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A	**Region 1**
	• Occurrence of RBC transfusions on/after Week 5 (proportion of patients)
	• Occurrence of G-CSF administration (proportion of patients)
	• A composite endpoint (MAHE; number of events for all components) defined to include:
	  • All-cause hospitalizations
	  • All-cause dose reductions
	  • Febrile neutropenia
	  • RBC transfusions on/after Week 5
	  • Prolonged severe (Grade 4) neutropenia (duration > 5 days)
		Region 2
		• Overall survival (will not be factored into multiplicity adjustment)
		• All-cause dose reductions (number of events)
		• Occurrence of RBC transfusions on/after Week 5 (proportion of patients)
		• Occurrence of G-CSF administration (proportion of patients)

SUPPORTIVE SECONDARY OBJECTIVES	**SUPPORTIVE SECONDARY ENDPOINTS**	

Evaluate potential of trilaciclib, compared with placebo, to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A	**All Regions**
	• (**Region 1 ONLY**) OS (analysis will focus on "do no harm")
	• **(Region 2 ONLY)** A composite endpoint (MAHE; number of events for all components) defined to include:
	  • All-cause hospitalizations
	  • All-cause dose reductions
	  • Febrile neutropenia
	  • RBC transfusions on/after Week 5
	  • Prolonged severe neutropenia (duration > 5 days)	

Evaluate the antitumor activity of trilaciclib or placebo administered in combination with E/P/A to patients with SCLC	• Occurrence of objective response (CR or PR per RECIST 1.1 as assessed by investigator) • Duration of objective response (CR or PR per RECIST v1.1 as assessed by investigator) • PFS (per RECIST 1.1 as assessed by investigator)
Determine the safety and tolerability of trilaciclib or placebo administered in combination with E/P/A in patients with SCLC	• Occurrence and severity of AEs by NCI CTCAE v4.03 • Occurrence and severity of AESIs for atezolizumab by NCI CTCAE v4.03 • Changes in laboratory parameters (hematology, chemistry, urinalysis), vital signs and ECG parameters • Grade 3 and 4 abnormalities in laboratory parameters (hematology and chemistry) • Occurrence and severity of infusion-related reactions • Occurrence of trilaciclib dose delays and interruptions • Occurrence of chemotherapy dose reductions • Occurrence of chemotherapy dose delays and interruptions • Occurrence of atezolizumab dose delays and interruptions • Relative dose intensity of carboplatin and etoposide • Occurrence of patients that discontinue study treatment because of AEs
Evaluate potential of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing effects on multiple lineages and current standard of care interventions to treat myelosuppression (neutrophils, RBC, platelets, lymphocytes)	• All-cause hospitalizations • Febrile neutropenia • G-CSF administration • Occurrence of Grade 3 and 4 hematologic lab values • ANC nadir by cycle • Prolonged severe neutropenia (duration >5 days) • Platelet transfusions • RBC transfusions • ANC, hemoglobin, platelet counts, and lymphocyte counts over time • Occurrence of ESA administration • Occurrence of systemic antimicrobial administration
Describe the PK of trilaciclib, carboplatin, and etoposide in a subset of patients; and atezolizumab in all patients	PK parameters will be calculated (as data permit) for trilaciclib, carboplatin, etoposide and atezolizumab: C_{max}, C_{min}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, CL, and V_z.
[redacted]	[redacted]



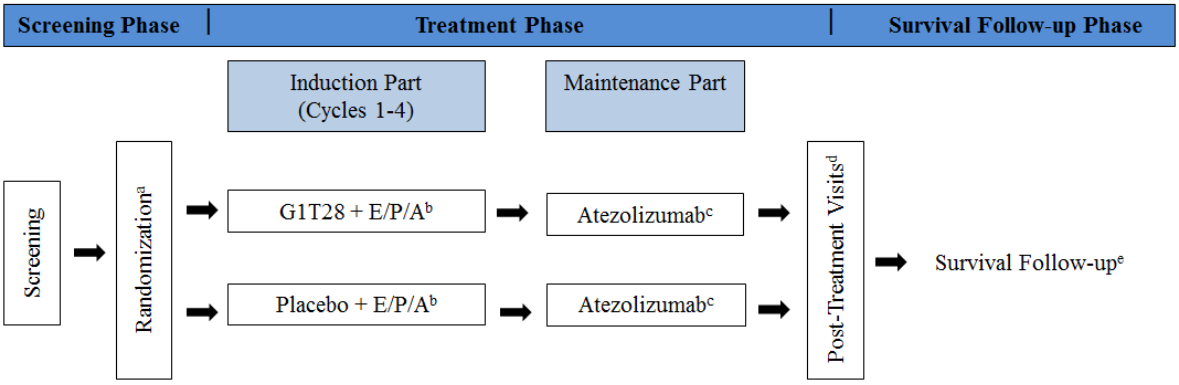
AE = adverse event; AESI = adverse event of special interest; ANC = absolute neutrophil count; CR = complete response; ATA = anti-atezolizumab antibodies; E/P/A = etoposide + carboplatin + atezolizumab; [redacted]; G-CSF = granulocyte-colony stimulating factor; irAE = immune-related adverse event; irRECIST = immune-related RECIST; MAHE = major adverse hematologic events; NCI CTCAE v4.03 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03; ORR = objective response rate; OS = overall survival; PD-1 = program cell death protein 1; PD-L1 = programmed death ligand 1; PK = pharmacokinetics; PFS = progression-free survival; PR = partial response; [redacted]; RBC = red blood cell; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SCLC = small cell lung cancer

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study of the efficacy and safety of E/P/A with trilaciclib or placebo therapy for patients with newly diagnosed extensive-stage SCLC. Approximately 100 patients will be randomly assigned (1:1 fashion) to trilaciclib 240 mg/m^2 or placebo administered IV on Days 1 to 3 with E/P/A therapy for up to four 21-day cycles (induction part) (Figure 6-1). Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no). Following the completion of up to 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles, patients will proceed to the maintenance part of the study and receive atezolizumab every 21 days. Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part. Treatment in both parts will continue until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit. The study includes 3 phases: Screening Phase, Treatment Phase (induction part + maintenance part), and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes after the last Post Treatment Visit.

Figure 6-1 Study Schema



CR = complete response; E/P/A = etoposide, carboplatin, and atezolizumab; irRECIST = immune-related RECIST; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease

a Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no).

b During the induction part of the study, trilaciclib or placebo + E/P/A therapy will continue for up to four 21-day cycles or until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. Tumors should be assessed after every even cycle (ie, approximately every 6 weeks) using RECIST, Version 1.1. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit (see Section 11.1.4). Assessments should be performed within 7 days of starting the subsequent cycle.

c Following induction, patients will proceed to the maintenance part of the study and receive atezolizumab every 21 days until disease progression per RECIST, Version 1.1, unacceptable toxicity, or discontinuation by the patient or investigator. Tumors should be assessed after every even cycle for the first 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit (see Section 11.1.4).

d All patients will return to the study center for post-treatment visits at 30 (+ 3) and 90 (+7) days after the last dose of study drug.

e The Survival Follow-up Phase will continue until at least 70% of the patients randomized in the study have died.

The initial diagnosis of SCLC should be made based on standard pathological examination, preferably including immunohistochemical staining for neuroendocrine features. Archived tumor samples should be available for banking for assessment of relevant DNA, ribonucleic acid (RNA), and protein markers, such as PD-L1 or those involved in the CDK4/6 pathway. Tumor samples may be banked for up to 10 years.

6.1.1. Criteria for Subsequent Cycles and Study Duration

Study drug administration will continue for up to 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles during the induction part of the study and atezolizumab will be administered every 21 days during the maintenance part of the study. Study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. However, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of

clinical benefit (see Section 11.1.4). Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for administrative reasons as described below.

In order to start Cycle 2 and subsequent cycles in the induction part up to Induction Cycle 4 as scheduled, patients should meet all of the following criteria:

- ANC $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline

A delay of > 9 weeks for recovery from any toxicity related to trilaciclib or placebo + E/P in order to meet the continuation criteria will result in discontinuation of trilaciclib or placebo + E/P. A delay of > 15 weeks for recovery and management of immune-related toxicities attributed to atezolizumab (12 weeks for recovery to $\leq$ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to $\leq$ 10 mg/day) will result in discontinuation of atezolizumab (see Section 8.4.5.3). If patients meet the criteria for starting the subsequent cycle, a delay of up to 2 weeks is permitted for administrative reasons (eg, holiday, vacation, etc.); however, a total delay of more than 9 weeks for trilaciclib or placebo + E/P, or 15 weeks for atezolizumab must be discussed with the medical monitor. [redacted]

Discontinuation or interruption of trilaciclib or placebo + E/P does not preclude continuation of atezolizumab and vice versa. For instance, if an AE is attributed to trilaciclib or placebo, etoposide, or carboplatin (eg, hematologic toxicity) during the induction part of the study; then atezolizumab will be continued while the trilaciclib or placebo + E/P are held. While the trilaciclib or placebo + E/P are held, the patient will continue to receive atezolizumab, be monitored for safety (see Section 10.3.4), and will begin the next trilaciclib or placebo + E/P/A-containing induction cycle after the toxicity resolves. If the AE is immune related and attributed to atezolizumab; then trilaciclib or placebo + E/P will be continued for up to 4 cycles while the atezolizumab is held.

After discontinuation of all study drugs, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, [redacted] CBC assessment on Day 22; all Post-Treatment Visits; and the Survival Follow-up Phase of the study, which is to continue until at least 70% of the patients on the study have died. The G1T28-05 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study.

The total study duration is at least 36 months, assuming 12 months of accrual and 24 months follow-up.

The Survival Follow-up Phase will continue until at least 70% of the randomized patients have died.

6.1.2. Safety Assessments

Safety assessments will include monitoring of AEs (including SAEs, irAEs and AESI), vital signs measurements, physical examinations, ECGs, performance status, clinical laboratory studies, and IRRs as described in Section 11.4. Safety surveillance reporting of AEs commences at the time of informed consent. AEs will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

6.1.3. Data Monitoring Committee

An independent data monitoring committee (DMC) will monitor accumulating safety and disposition data after approximately 12 patients have been enrolled and have completed at least 1 cycle to assess the initial safety data from the 2 groups, and then approximately every 4 months during the Treatment Phase of the study, depending upon the enrollment rate. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

6.1.4. Tumor Assessment

Tumor assessments using radiologic imaging will be performed after every even cycle (ie, approximately every 6 weeks) for the first 9 months of the study and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug. Tumor assessments will include tumor response based on RECIST v1.1 and irRECIST. For tumor assessment, all sites of disease should be assessed radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) at screening and every scheduled tumor assessment until the occurrence of disease progression. CT or MRI scans obtained as standard of care prior to informed consent will not need to be repeated if performed within 14 days prior to dosing. Brain scans performed as standard of care prior to informed consent will not need to be repeated if performed within 28 days prior to dosing. Assessments should be performed within 7 days prior to starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. For patients who have a confirmed CR, it is strongly recommended that they receive prophylactic cranial irradiation (PCI) after completion of chemotherapy (ie, induction). Patients with a confirmed PR should also consider PCI after completion of chemotherapy (ie, induction) based on the investigator's judgment (see Section 8.8). Following the completion of the induction part, PCI may be administered concurrently with atezolizumab during the maintenance part. For those patients who have not progressed at the time of study drug discontinuation, tumor assessments to include all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission

tomography (PET) is used, it should also be accompanied by spiral CT or MRI. Tumor assessment is further described in Section 11.1.

7. STUDY POPULATION

7.1. Selection of Patients

Overall, approximately 100 patients will be randomly assigned (1:1 ratio) to 1 of 2 groups as follows: trilaciclib administered IV with E/P/A therapy followed by atezolizumab maintenance (Group 1) or placebo administered IV with E/P/A therapy followed by atezolizumab maintenance (Group 2).

The study will be conducted at up to 60 centers in North America and Europe.

7.1.1. Inclusion Criteria

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

1. Age ≥ 18 years
2. Unequivocally confirmed diagnosis of SCLC by histology or cytology, preferably including the presence of neuroendocrine features by immunohistochemistry
3. Extensive-stage SCLC
4. At least 1 target lesion that is measurable by RECIST v1.1 (Eisenhauer 2009)
5. Hemoglobin ≥ 9.0 g/dL
6. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
7. Platelet count ≥ 100×10^9/L
8. Creatinine ≤ 1.5 mg/dL or glomerular filtration rate (GFR) of ≥ 60 mL/minute
9. Total bilirubin ≤ 1.5 × ULN; < 3 × ULN if the patient has documented Gilbert's disease
10. AST and ALT ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases
11. ECOG performance status of 0 to 2
12. Predicted life expectancy of ≥ 3 months
13. Contraception:
    a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening. Females must be either postmenopausal, surgically sterile, or agree to use 2 forms of highly effective contraception during the study and for 6 months following discontinuation of study treatment

i. Postmenopausal is defined as (1) at least 60 years of age, (2) medically confirmed ovarian failure, or (3) younger than 60 years of age and have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and/or serum levels of estradiol and follicle stimulating hormone within the laboratory's reference range for postmenopausal females
ii. Acceptable surgical sterilization techniques are complete or partial hysterectomy, bilateral tubal ligation with surgery at least 6 months prior to dosing, or bilateral oophorectomy with surgery at least 2 months prior to dosing
iii. Highly effective methods of contraception are those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. These include the following:
    1. Established use of oral, injected or implanted hormonal methods of contraception (stable dose at least 3 months prior to dosing)
    2. Placement of an intrauterine device or intrauterine system
    3. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) **with** spermicidal foam/gel/film/cream/suppository. *Barrier methods alone (without spermicide) are not acceptable methods. Likewise, spermicide alone is not an acceptable method*
    4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). *For female patients on the study, the vasectomized male partner should be the sole partner for that patient*
    5. True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

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

14. Able to understand and sign an informed consent

7.1.2. Exclusion Criteria

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

1. Limited-stage SCLC

2. Prior chemotherapy for limited or extensive-stage SCLC

3. Prior treatment with immunotherapies including but not limited to cluster of differentiation 137 (CD137) agonists or immune checkpoint blockade therapies (such as anti-PD-1, anti-PD-L1, CTLA4 therapeutic antibodies)

4. Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids

5. Malignancies other than SCLC within 3 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome

6. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan (history of radiation pneumonitis in the radiation field [fibrosis] is permitted)

7. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Exceptions include vitiligo, controlled asthma, type I diabetes, Graves' disease, Hashimoto's disease, or with medical monitor approval. Stable replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) for well-controlled disease is not considered a form of systemic treatment.

8. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (Class III or IV as defined by the New York Heart Association [NYHA] functional classification system)

9. Known history of stroke or cerebrovascular accident within 6 months prior to enrollment

10. Serious active infection at the time of enrollment

11. Psychiatric illness/social situations that would limit study compliance

12. Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol

13. Known human immunodeficiency virus (HIV), known active Hepatitis B (eg, HBsAg reactive or HBV DNA detected) or Hepatitis C (eg, HCV RNA [qualitative] is detected)

14. Radiotherapy to any site within 2 weeks prior to enrollment

15. Receipt of any investigational medication within 4 weeks prior to enrollment

16. Administration of a live attenuated vaccine within 4 weeks before enrollment or anticipation that such a live attenuated vaccine will be required during the study

17. Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (eg, FluMist) within 4 weeks prior to enrollment, at any time during the study, and at least 5 months after the last dose of atezolizumab

18. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

19. Hypersensitivity to any of the components of the formulation of etoposide or etoposide phosphate

20. Hypersensitivity to carboplatin or other platinum-containing compounds, or mannitol

21. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

22. Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies

23. Legal incapacity or limited legal capacity

24. Pregnant or lactating women

Patients may withdraw from study drug or from the study at their own discretion (or at the discretion of the investigator) for any reason at any time (see Section 12.3 and 12.4).

8. TREATMENTS

8.1. Treatments Administered

In the induction part of the study, patients will receive trilaciclib 240 mg/m^2 or placebo administered IV once daily on Days 1 to 3 of each 21-day E/P/A therapy cycle (up to 4 cycles in total). In the maintenance part of the study, patients will receive atezolizumab every 21 days.

Patients will receive E/P/A therapy in 21-day cycles during the induction part of the study. The carboplatin dose will be calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV over 30 minutes on Day 1, and 100 mg/m^2 etoposide will be administered IV over 60 minutes daily on Days 1, 2, and 3 of each 21-day cycle. Atezolizumab 1200 mg in 250 mL sodium chloride solution 0.9% will be administered as an IV infusion on Day 1 of each 21-day cycle in both the induction and maintenance parts. Atezolizumab should be infused over 60 minutes for the first administration and, if tolerated, all subsequent infusions may be delivered over 30 minutes. Atezolizumab should be administered following the completion of administration of trilaciclib or placebo, etoposide, and carboplatin.

There will be no intrapatient dose modifications of trilaciclib or atezolizumab during the study. Dose modifications allowed for E/P are described in Section 8.4.5.

The interval between doses of trilaciclib or placebo on successive days should not be greater than 28 hours. The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours.

Trilaciclib or placebo will only be administered with E/P therapy. If administration of E/P therapy is held or discontinued, trilaciclib or placebo will also be held or discontinued.

Chemotherapy cannot be administered until after completion of the trilaciclib or placebo infusion. If the second or third dose of trilaciclib or placebo in any given cycle is not administered for any reason, do not administer the dose of etoposide chemotherapy on that day, since this could potentially exacerbate myelosuppression (see Section 4.5).

In both parts of the study, study drug administration will continue until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit (see Section 11.1.4). Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for up to a 2-week delay for administrative reasons; however, a total delay of more than 9 weeks for trilaciclib or placebo +E/P, or 15 weeks for atezolizumab must be discussed with the medical monitor. If the subsequent cycle is delayed, the patient should still complete the clinical laboratory

assessments [redacted] on the scheduled Day 1, as well as on the actual first dosing day of the next cycle.

Patients should meet the requirements outlined in Section 6.1.1 before initiation of Cycle 2 and each subsequent induction cycle of therapy.

8.2. Investigational Products

Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part.

8.2.1. Identity

8.2.1.1. Trilaciclib

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

8.2.1.2. Placebo

The placebo formulation of 250 mL of dextrose 5% in water (D5W) or sodium chloride solution 0.9% will be prepared by the pharmacist/designee on site.

8.2.1.3. Etoposide and Carboplatin

Descriptions of the formulations of commercially-available etoposide and carboplatin can be found in the respective current prescribing information (see Appendix 4).

8.2.1.4. Atezolizumab

A description of the formulation of atezolizumab can be found in the current prescribing information (see Appendix 2).

8.2.2. Packaging and Labeling

8.2.2.1. Trilaciclib

Trilaciclib Sterile Powder, 300 mg per vial is manufactured and packaged by [redacted].

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

8.2.2.2. Placebo

The placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% will be prepared by the pharmacist/designee on site, and labeled with the randomization number.

8.2.2.3. Etoposide and Carboplatin

Descriptions of the packaging and labeling of commercially-available carboplatin and etoposide can be found in the respective current prescribing information (see Appendix 4).

8.2.2.4. Atezolizumab

A description of the packaging and labeling of atezolizumab can be found in the current prescribing information (see Appendix 2).

8.2.3. **Storage**

8.2.3.1. Trilaciclib

Study drugs will be stored [redacted] under applicable storage conditions at the site and only the pharmacist/designee and designated personnel will have access to the study drugs. Storage conditions of trilaciclib are detailed in the pharmacy manual.

8.2.3.2. Placebo

The placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% will be stored identically to trilaciclib to protect the integrity of the blind.

8.2.3.3. Etoposide and Carboplatin

Information regarding the storage of commercially-available carboplatin and etoposide can be found in the respective current prescribing information (see Appendix 4).

8.2.3.4. Atezolizumab

Information regarding the storage of atezolizumab can be found in the current prescribing information (see Appendix 2).

8.2.4. **Procedure for Dispensing**

Dispensing instructions, including instructions for masking the trilaciclib or placebo infusion bags and tubing will be provided in the Pharmacy Manual and will be maintained in the pharmacy records.

8.2.5. **Investigational Product Accountability**

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

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

- Date received
- Lot number

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

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

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

8.3. Method of Assigning Patients to Treatment Groups

A unique patient identification number (screen number) will be assigned to each patient who signs an informed consent form. Patients meeting all inclusion and exclusion criteria will be randomized 1:1 to receive trilaciclib or placebo with E/P/A therapy during the induction part as described in Section 8.5. Each enrolled patient will be assigned a unique randomization number by an interactive web-response system (IWRS); this number will be unique and will not be reused.

8.4. Dose, Dosing Regimen, and Route

8.4.1. Trilaciclib

Trilaciclib 240 mg/m^2 diluted in 250 mL of D5W or sodium chloride solution 0.9% is to be administered by IV infusion over approximately 30 minutes. If there is any study drug remaining in the infusion bag at the end of the 30 minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. Details regarding the reconstitution and dilution of trilaciclib vials are detailed in the Pharmacy Manual.

The interval between doses of trilaciclib on successive days should not be greater than 28 hours. Trilaciclib will only be administered with E/P therapy. If administration of E/P therapy is held or discontinued, trilaciclib will also be held or discontinued.

8.4.2. Placebo

The placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% will be administered over approximately 30 minutes. If there is any volume remaining in the infusion bag at the end of the 30 minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose.

The interval between doses of placebo on successive days should not be greater than 28 hours. Placebo will only be administered with E/P therapy. If administration of E/P therapy is held or discontinued, placebo will also be held or discontinued.

8.4.3. Etoposide and Carboplatin

Etoposide and carboplatin will be administered IV in accordance with the prescribing information (see Appendix 4) and according to the study site's standard practice.

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

The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours.

Chemotherapy cannot be administered until after completion of the trilaciclib or placebo infusion. If the second or third dose of trilaciclib in any given cycle is not administered for any reason, do not administer the dose of etoposide chemotherapy on that day, since this could potentially exacerbate myelosuppression (see Section 4.5).

8.4.3.1. Carboplatin

The carboplatin dose will be calculated using the Calvert formula with a target AUC = 5 on Day 1 of each 21-day cycle and administered as an IV infusion over 30 to 60 minutes (per institutional standard of care). The Calvert formula is as follows:

Total carboplatin dose (mg) = (target AUC) × (GFR + 25)

Because the estimated GFR may be based on serum creatinine measurements obtained using standardized isotope dilution mass spectrometry, the **dose of carboplatin should be capped at 750 mg** to avoid potential toxicity due to overdosing. The cap dose of 750 mg for carboplatin is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function (ie, maximum carboplatin dose = target AUC of 5 mg•min/mL × 150 mL/min = 750 mg).

The weight used for calculation of GFR using the Cockcroft-Gault equation should be the actual body weight (and not ideal body weight).

Refer to the carboplatin prescribing information (see Appendix 4) for details regarding preparation, administration, instructions and precautions. Premedications may be provided per local standard of care.

8.4.3.2. Etoposide

Etoposide 100 mg/m^2 will be administered as an IV infusion over 60 minutes on Days 1, 2, and 3 of each 21-day cycle.

Refer to the etoposide prescribing information (see Appendix 4) for details regarding preparation, administration, instructions, and precautions.

8.4.4. Atezolizumab

Atezolizumab 1200 mg will be administered as an IV infusion on Day 1 of each 21-day cycle. The first dose should be administered over 60 minutes and, if it is tolerated, subsequent doses may be administered over 30 minutes. For the first 4 cycles, ie, during the induction part, atezolizumab should be administered following the administration of trilaciclib or placebo, etoposide and carboplatin.

Refer to the atezolizumab prescribing information (see Appendix 2) for details regarding preparation, administration, instructions, and precautions.

8.4.5. Dose Modifications

8.4.5.1. Trilaciclib

To ensure the greatest level of safety when trilaciclib is coadministered with chemotherapeutic agents, the magnitude and duration of trilaciclib-induced HSPC arrest was simulated using a PK/pharmacodynamic model and verified by performing bone marrow cell cycle analysis before or after administration of trilaciclib IV at 192 mg/m^2 to different groups of human subjects in the Phase 1a Study G1T28-1-01. Trilaciclib at a dose of 192 mg/m^2 (rounded to 200 mg/m^2 for this study) demonstrated robust bone marrow HSPC arrest for > 24 hours and was determined to be the BED (Section 4.3.1). It is unknown if lower doses will produce the same magnitude and duration of HSPC cell cycle arrest. Insufficient HSPC arrest (ie, for too short a duration) could result in the release of HSPCs into the S (DNA synthesis) phase of the cell cycle while chemotherapy is present, thereby potentially exacerbating myelosuppression. However, higher doses of trilaciclib (240 and 280 mg/m^2) have been tested in patients with SCLC. Based on the Phase 1b results from these subsequent Phase 1b/2a SCLC studies (G1T28-02 [administered prior to etoposide and carboplatin] and G1T28-03 [administered prior to topotecan]), trilaciclib 240 mg/m^2 was chosen as the recommended Phase 2 dose. **Therefore, to minimize this risk of an insufficient HSPC arrest, the dose of trilaciclib will not be modified and will remain at 240 mg/m^2 throughout the study**.

8.4.5.2. Modification of Etoposide and Carboplatin Dosing

Patients should meet the laboratory parameter requirements outlined in Section 10.3.2 before initiation of Cycle 2 and each subsequent cycle of E/P therapy. All nonhematologic drug-related toxicities (except alopecia) should have resolved to Grade 1 or baseline before initiation of the next cycle of E/P therapy.

Dose adjustments are to be made according to the organ system showing the greatest degree of drug-related toxicity. Toxicities will be graded using NCI CTCAE, Version 4.03. Initiation of the next cycle of trilaciclib or placebo + E/P therapy may be delayed by no more than 9 weeks to allow recovery from toxicity due to the chemotherapy agents. A treatment delay of > 9 weeks due to trilaciclib or placebo + E/P toxicity will lead to discontinuation of trilaciclib or placebo + E/P therapy.

No more than 2 dose reductions of E/P in total are allowed for any patient. Simultaneous reduction in the doses of etoposide and carboplatin will count as 1 dose reduction. Toxicity

that requires dose reduction more than twice will lead to discontinuation of trilaciclib or placebo + E/P therapy. Under this circumstance, administration of trilaciclib or placebo should also be discontinued. All dose reductions are permanent and no dose increases are allowed.

Since fatigue can be a symptom of cancer progression, dose reduction will only be performed if it is deemed to be drug-related in the opinion of the investigator.

The dose reductions in Table 8-1 will be utilized for the purpose of dose modifications for toxicity.

Table 8-1 Etoposide and Carboplatin Dose Reductions

Dose level	Etoposide (mg/m^2)	Carboplatin (AUC)
Dose level -1 (first dose reduction)	Reduce to 75 mg/m^2	Reduce to AUC = 4
Dose level -2 (second dose reduction)	Reduce to 50 mg/m^2	Reduce to AUC = 3

AUC = area under the concentration-time curve

Dose Modifications for Hematologic Toxicity

First Day of Induction Cycle 2 and Beyond

In order to start Induction Cycle 2 and subsequent induction cycles as scheduled, on Day 1 of the cycle, patients must have an ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline. The dose adjustments in Table 8-2 are based on the ANC and platelet counts on the first day of treatment for Cycle 2 and each subsequent induction cycle.

Table 8-2 Etoposide and Carboplatin Dose Adjustments Based on Lack of Recovery of Absolute Neutrophil or Platelet Counts on the First Day of Induction Cycle 2 and Each Successive Cycle

Absolute Neutrophil Count < 1.5 × 10^9/L	**Etoposide**	**Carboplatin**
First episode	No change. Use G-CSF with subsequent cycles. Refer to the American Society of Clinical Oncology (ASCO) guidelines (Smith 2015).	No change. Use G-CSF with subsequent cycles. Refer to ASCO guidelines (Smith 2015).
Second episode	First dose reduction	First dose reduction
Third episode	Second dose reduction	Second dose reduction
Fourth episode	Discontinue drug	Discontinue drug
Platelet Count < 100 x 10^9/L	**Etoposide**	**Carboplatin**
First episode	First dose reduction	First dose reduction
Second episode	Second dose reduction	Second dose reduction
Third episode	Discontinue drug	Discontinue drug

G-CSF = granulocyte colony-stimulating factor

Neutrophils

The dose adjustments in Table 8-3 are based on the ANC nadir with or without fever during the preceding treatment cycle.

Table 8-3 Etoposide and Carboplatin Dose Adjustments Based on Absolute Neutrophil Count Nadir With or Without Fever

ANC Nadir	Etoposide	Carboplatin
Grade 3[a] (without fever)	No Change	No change
Grade 4[b] for ≥ 7 days (without fever)		
First episode	No change. Use G-CSF with subsequent cycles. Refer to the ASCO guidelines (Smith 2015).	No change. Use G-CSF with subsequent cycles. Refer to ASCO guidelines (Smith 2015).
Second episode	First dose reduction	First dose reduction
Third episode	Second dose reduction	Second dose reduction
Fourth episode	Discontinue drug	Discontinue drug
Grade 3/4 with fever		
First episode	No change. Use G-CSF with subsequent cycles. Refer to the ASCO guidelines (Smith 2015).	No change. Use G-CSF with subsequent cycles. Refer to ASCO guidelines (Smith 2015).
Second episode	First dose reduction	First dose reduction
Third episode	Second dose reduction	Second dose reduction
Fourth episode	Discontinue drug	Discontinue drug

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor

[a] Grade 3 ANC: 500 to < 1000/mm^3

[b] Grade 4 ANC: < 500/mm^3

Platelets

The dose adjustments in Table 8-4 are based on the platelet nadir during the preceding treatment cycle.

Table 8-4 Etoposide and Carboplatin Dose Adjustment Based on Platelet Nadir

Platelet Count Nadir	Etoposide	Carboplatin
Grade 4[a] or ≥ Grade 3[b] with bleeding		
First episode	First dose reduction	First dose reduction
Second episode	Second dose reduction	Second dose reduction
Third episode	Discontinue drug	Discontinue drug

[a] Grade 4 platelet count: <25,000/mm^3

[b] Grade 3 platelet count: 25,000 to < 50,000/mm^3

Colony Stimulating Factors

Patients will not receive colony stimulating factors (CSFs; eg, granulocyte colony stimulating factor [G-CSF]; granulocyte-macrophage colony-stimulating factor [GM-CSF]) or erythropoiesis stimulating agents (ESAs) during Induction Cycle 1 (ie, prior to the actual Cycle 2 Day 1 dosing visit).

Although CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia in any cycle, they may be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes (including in Induction Cycle 1 if necessary). Subsequent use **after Induction Cycle 1** will be based on toxicities as outlined above. Please also refer to the ASCO guidelines (Smith 2015) for neutropenia.

When indicated, as outlined above in Table 8-2 and Table 8-3, either filgrastim or pegfilgrastim may be used per the prescribing information. In the event a patient has a neutropenic event requiring G-CSF in the subsequent cycle, then filgrastim or pegfilgrastim should not be initiated until at least 24 hours after dosing of the next subsequent cycle is complete (ie, no earlier than Day 4 of the next subsequent cycle). Filgrastim or pegfilgrastim should not be used to increase low neutrophil counts mid-cycle or prior to the start of the subsequent cycle.

For a hemoglobin level < 9.0 g/dL or symptomatic anemia when indicated, epoetin alfa or darbepoetin alfa may be used to treat patients per the prescribing information.

8.4.5.2.1. Dose Modifications for Nonhematologic Toxicity

Hepatic Toxicity

The following dose adjustments for etoposide and carboplatin are based on serum AST/ALT and bilirubin levels (Table 8-5) during the preceding treatment cycle.

Table 8-5 Etoposide and Carboplatin Reduction for Hepatic Toxicity

AST/ALT		Bilirubin	Etoposide	Carboplatin
Grade 1	and/ or	≤ Grade 2	No change	No change
≥ Grade 2	and/or	≥ Grade 3		
First episode		First episode	First dose reduction	First dose reduction
Second episode		Second episode	Second dose reduction	Second dose reduction
Third episode		Third episode	Discontinue drug	Discontinue drug

For patients enrolled with baseline AST and ALT ≥ 3 × ULN in the presence of liver metastases, if further increase in AST and ALT occurs, trilaciclib or placebo + E/P should be held until the patient is discussed with the medical monitor.

Gastrointestinal toxicity

Nausea and vomiting should be managed with the use of adequate antiemetic therapy. Prophylactic anti-emetic therapy can be used at the discretion of the treating physician. Dexamethasone should be avoided as an antiemetic, if possible. Patients are encouraged to take plenty of oral fluids.

Diarrhea should be managed with appropriate antidiarrheal therapy. Patients should be encouraged to take plenty of oral fluids.

Hypersensitivity Reactions

For patients who had a mild to moderate hypersensitivity reaction and have been successfully re-challenged, careful attention to prophylaxis and bedside monitoring of vital signs is recommended for all subsequent doses.

Mild symptoms (eg, mild flushing, rash, pruritus): complete infusion. Supervise at bedside. No treatment required.

Moderate symptoms (eg, moderate rash, flushing, mild dyspnea, chest discomfort): stop infusion. Give IV diphenhydramine 25 mg and IV dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate, 20 mg/hour. If no further symptoms occur after 15 minutes, the rate may be increased to the full rate until the infusion is complete. If symptoms recur, the infusion must be stopped. The patient should receive no additional etoposide or carboplatin for that cycle, but may receive additional doses at the discretion of the investigator.

Severe life-threatening symptoms (eg, hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticarial): stop infusion immediately. Give IV diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to bronchodilators, epinephrine is recommended. Patient should not receive any further doses of etoposide or carboplatin. Report this occurrence as an AE.

Other Toxicities

For the first occurrence of any nonhematologic Grade 2 chemotherapy-related toxicity (except alopecia), trilaciclib or placebo + E/P should be withheld until the toxicity recovers to Grade 1 or baseline. Treatment may then be resumed at the same dose level. For the second occurrence of any nonhematologic Grade 2 chemotherapy-related toxicity (except alopecia), following recovery of the toxicity to Grade 1 or baseline, E/P should be resumed at dose level -1; for the third occurrence, the E/P doses should be reduced to dose level -2. A fourth occurrence will result in discontinuation of trilaciclib or placebo + E/P therapy. No dose reduction should be made for Grade 1 toxicities.

For any Grade 3 or 4 chemotherapy-related toxicities not mentioned above, trilaciclib or placebo + E/P should be withheld until the toxicity recovers to Grade 1 or baseline. Treatment should then be resumed at dose level -1 for the first occurrence and dose level -2 for the second occurrence. A third occurrence will result in discontinuation of trilaciclib or placebo + E/P therapy.

8.4.5.3. Atezolizumab

A list of the AESI for atezolizumab is provided in Appendix 3 and these should be reported using the same process and timeline as SAE reporting (see Section 11.4.1.10).

No dose reductions will be allowed for atezolizumab during the study. Management of irAEs may include administration of corticosteroids, delay of a scheduled dose, or discontinuation of therapy. Please refer to the Atezolizumab Guidance for the Investigator (Appendix 1) and the full atezolizumab prescribing information (Appendix 2) for guidance on the management of irAEs.

Atezolizumab has been associated with risks such as the following: IRRs; immune-related hepatitis, pneumonitis, colitis, pancreatitis; diabetes mellitus; hypothyroidism; hyperthyroidism; adrenal insufficiency; Guillain-Barré syndrome; myasthenic syndrome or myasthenia gravis; hypophysitis; and meningoencephalitis. In addition, systemic immune activation is a potential risk associated with atezolizumab when given in combination with other immunomodulating agents. Refer to the Atezolizumab Guidance for the Investigator (Appendix 1) for a detailed description of anticipated safety risks for atezolizumab and their management.

For patients enrolled with baseline AST and ALT $\geq$ 3 x ULN in the presence of liver metastases, if further increase in AST and ALT occurs, atezolizumab should be held until the patient is discussed with the medical monitor.

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

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

Other irAEs attributed to atezolizumab not listed above should be assessed by the investigator and discussed with the medical monitor to determine if atezolizumab should be held or discontinued.

If corticosteroids have been initiated as part of the irAE management, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If the delay for re-starting atezolizumab is > 15 weeks for recovery from immune-related toxicities attributed to atezolizumab (12 weeks for recovery to ≤ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to ≤ 10 mg/day), atezolizumab will be permanently discontinued.

Discontinuation or interruption of trilaciclib or placebo + E/P does not preclude continuation of atezolizumab and vice versa. For instance, if an AE is attributed to trilaciclib or placebo, etoposide, or carboplatin (eg, hematologic toxicity) during the induction part of the study, then atezolizumab will be continued while the trilaciclib or placebo + E/P are held. While the trilaciclib or placebo + E/P are held, the patient will continue to receive atezolizumab, be monitored for safety (see Section 10.3.4), and will begin the next trilaciclib or placebo + E/P/A-containing induction cycle after the toxicity resolves. If the AE is immune related and attributed to atezolizumab; then trilaciclib or placebo + E/P will be continued for up to 4 induction cycles while the atezolizumab is held.

8.5. Randomization and Blinding

The study is randomized and blinded. Patients meeting all inclusion and exclusion criteria will be randomized 1:1 to receive trilaciclib or placebo with E/P/A therapy by an IWRS according to a randomization schedule generated by an unblinded statistician. Randomization will be stratified by ECOG performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no). Each patient will be assigned a unique randomization number, which will not be reused.

Each site will have an unblinded pharmacist/designee, who will have access to the treatment assignment to label and distribute the blinded study drug. 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 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 will

obtain the treatment assignment details from the IWRS. Any unplanned unblinding must be communicated to the project manager and study statistician for documentation in the study files and the clinical study report.

8.6. Prior and Concomitant Medications and Procedures

All concomitant medications including prescription medications, over-the-counter preparations, growth factors, blood products, and parenteral nutrition taken during the 14 days before the date of enrollment, during the study treatment, and through 30 days after the last dose of study drug will be documented. Documentation will include information regarding start and stop dates, dose(s), and reasons for the medication use.

Administration of other concomitant nonprotocol anticancer therapies prior to progression is not permitted while on this study.

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

Palliative radiation therapy or surgery is allowed to control disease symptoms but not to aid in the response of the tumor and patients requiring palliative radiation may continue receiving study drug administration if they meet the requirements described in Section 11.1.4. However, for patients who have not had disease progression, the requirement for palliative radiation therapy or surgery will be regarded as disease progression.

Caution should be exercised when administering etoposide phosphate with drugs that are known to inhibit phosphatase activities (eg, levamisole hydrochloride). Although carboplatin has limited nephrotoxic potential, caution should be exercised when administering carboplatin with aminoglycosides, which has resulted in increased renal and/or audiologic toxicity. Any medication that is contraindicated when using etoposide or carboplatin is not permitted, and special warnings and precautions for use of carboplatin and etoposide should be observed.

Necessary supportive care such as antiemetics, antidiarrheals, etc., per the standard of care at the study center will be permitted. **Administration of hematopoietic growth factors in Induction Cycle 1 will not be permitted (ie, no growth factors should be used prior to the actual Induction Cycle 2 Day 1 dosing visit; Section 8.4.5.2).** However, hematopoietic growth factors may be utilized in subsequent cycles at the investigator's discretion as stated in Section 8.4.5.2. To reduce potential immune system interactions, the use of dexamethasone as an antiemetic should be minimized where possible.

For the purposes of this trial, concomitant medications like bisphosphonates and denosumab, which are used to prevent skeletal-related events in patients with bony metastases, are allowed as long as the patient has been on stable doses for at least 4 weeks.

Trilaciclib is a time-dependent inhibitor of CYP3A4 and is a substrate for CYP3A4. Trilaciclib exposure may be altered by concomitant use of drugs that are strong CYP3A inhibitors or inducers. The exposure of drugs that are CYP3A substrates may be altered by concomitant use of trilaciclib (Section 4.4.2).

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

Trilaciclib is a potent inhibitor of MATE1, MATE2-K, OCT2 membrane transporters and therefore caution should be exercised with concomitant use of drugs that are substrates for these transporters (Section 4.4.2).

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted. There are no known interactions with other medicinal products or other form of interactions (Section 1.10 of the Atezolizumab Guidance for the Investigator, Appendix 1).

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

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.

Medications will be coded using the most recent World Health Organization (WHO) Drug Dictionary version.

8.7. Transfusions

Platelets should be transfused at a threshold of ≤ 10,000/μL. Platelets should also be transfused in any patient who is bleeding with a platelet count < 50,000/μL (100,000/μL for central nervous system or ocular bleeding). Please also refer to the American Society of Clinical Oncology (ASCO) guidelines (Schiffer 2001).

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

8.8. Prophylactic Cranial Irradiation

Prophylactic cranial irradiation for patients without detectable brain metastases has been shown to decrease the frequency of subsequent intracranial relapse and improve survival for patients with SCLC (Aupérin A 1999; Slotman 2007). Therefore, patients with a confirmed CR are strongly encouraged to receive PCI after completion of induction chemotherapy. Patients with a confirmed PR should also consider PCI after completion of induction chemotherapy based on the investigator's judgment. Following the completion of the induction part, PCI may be administered concurrently with atezolizumab during the maintenance part.

8.9. 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 investigator or other study staff will supervise each dose of the study drugs administered in the clinic. 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 BSA; date and time of the start and end of each trilaciclib or placebo, etoposide, carboplatin, and atezolizumab infusion; and total drug administered in milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy will be recorded on the electronic case report form (eCRF) and in the source documents.

9. STUDY FLOWCHART

The procedures and assessments to be performed during the study are outlined in Table 9-1. The timing and number of samples collected for PK, immunologic markers and anti-atezolizumab antibody testing may be altered based on emerging data without requiring an amendment if the blood volume/day or overall does not increase and the patient is not required to have additional clinic visits or prolongation of a clinic visit, ie, the risk-benefit profile for the patient does not worsen. The investigators and institutional review boards (IRBs) or Independent Ethics Committees (IECs) will be notified if the frequency is reduced.

Table 9-1 Schedule of Assessments

	Screen-ing	Enroll	Induction (21-day cycles)[a]										Last Induc-tion Cycle	Maintenance (21-day cycles)[b]		Post-Treatment Visits[c]		Survival Follow-up[d]
			Induction Cycles 1 and 3					Induction Cycles 2 and 4						Maintenance Cycle 1 and Odd Cycles	Maintenance Cycle 2 and Even Cycles			
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**	**22**	**1**	**1**	**30 (+3)**	**90 (+7)**	
Informed Consent[e]	X																	
Demographics	X																	
Medical History[f]	X																	
Eligibility Eval.	X	X																
Performance Status	X		X					X						X	X	X	X	
Physical Exam	X		X					X						X	X	X	X	
Height, Weight & Vital Signs[g]	X		X		X			X		X				X	X	X	X	
Electrocardiogram	X												X					
Clinical Chemistry	X		X[h]					X[h]						X[h]	X[h]	X	X	
TSH, free T4, and free T3	X							X							X	X	X	
Hematology	X		X[i]		X	X	X	X[i]		X	X	X	X	X[i]	X[i]	X	X	
Urinalysis	X		X[h]					X[h]						X[h]	X[h]	X	X	
Pregnancy test[j]		X[j]														X	X	
Randomization[k]		X																
Tumor Assessment[l]	X[l2]											X			X	X[l1,l2]	X[l1,l2]	X[l1]
Archived Tumor Sample[m]		X																
Trilaciclib or Placebo[n]			X	X	X			X	X	X								
Carboplatin			X					X										
Etoposide			X	X	X			X	X	X								
Atezolizumab			X[o]					X[o]						X	X			
[redacted]			[redacted]					[redacted]						[redacted]	[redacted]	[redacted]	[redacted]	
PK[q] (Trilaciclib, Etoposide, Carboplatin)			X															

	Screen-ing	Enroll	Induction (21-day cycles)[a]										Last Induc-tion Cycle	Maintenance (21-day cycles)[b]		Post-Treatment Visits[c]		Survival Follow-up[d]
			Induction Cycles 1 and 3					Induction Cycles 2 and 4						Maintenance Cycle 1 and Odd Cycles	Maintenance Cycle 2 and Even Cycles			
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**	**22**	**1**	**1**	**30 (+3)**	**90 (+7)**	
Atezolizumab PK[r]			X					X							X	X	X	
Immunologic Marker[s]			X[s]											X[s]			X[s]	
Anti-atezolizumab Antibody Testing[t]			X					X							X	X	X	
AEs[u]	X[u]	X[u]															X[u]	
Con. Medications	X	X																
Survival Follow-up[d]																		X

AE = adverse event; Eval. = evaluation; [redacted]; irRECIST = immune-related RECIST; [redacted]; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = tri-iodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

a During the induction part, study drug administration (trilaciclib or placebo plus E/P/A) will continue for up to four 21-day cycles or until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit.

b During the maintenance part, study drug administration (atezolizumab) will continue in 21-day cycles until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurs first. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit.

c Patients will return to the study center for post-treatment visits at 30 (+3) and 90 (+7) days after the last dose of study drug.

d Monthly phone calls will be made to each patient that is in the Survival Follow-up Phase. Patients will be followed for survival until at least 70% of the patients have died. Any anticancer therapies used will be collected.

e Informed consent may be obtained up to 28 days prior to the first study treatment administration.

f Including medical, surgical, radiation history, smoking history, family history, documentation of tumor diagnosis, baseline signs and symptoms within 4 weeks prior to randomization, weight loss in the 6 months prior to randomization (≤ 5% or > 5%), and medications taken within 14 days of enrollment.

g Height will only be measured at the screening visit. Weight will only be measured at the screening visit and on Day 1 of each cycle. Body surface area calculation (based on actual body weight) will be completed on Day 1 of each cycle and vital signs obtained within 15 minutes before and after trilaciclib or placebo and E/P/A infusions. Vitals only need to be taken before the trilaciclib or placebo infusion, between each subsequent infusion, and after the last infusion on Days 1 and 3.

h Clinical chemistry (albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase [LDH], sodium, and blood urea nitrogen [BUN], amylase, lipase) and urine analysis may be obtained up to 72 hours prior to the first dose of each cycle of trilaciclib or placebo + E/P/A therapy (induction part) or atezolizumab (maintenance part).

i Hematology will be obtained (hemoglobin, white blood cells (WBC) with differential, and platelet counts). Hematology may be obtained up to 24 hours prior to first dose of each cycle of trilaciclib/placebo + E/P/A therapy (induction part) or atezolizumab (maintenance part).

j For female patients of childbearing potential: serum ß-hCG at enrollment; and serum or urine ß-hCG obtained at the post-treatment visits.

k Randomization is to be done within 3 days prior to first dose of trilaciclib or placebo + E/P/A therapy, following confirmation that the patient is eligible for the study.

l For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle for 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug, until the occurrence of disease progression. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. Assessments should be performed within 7 days of starting the subsequent cycle. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

l1: At the post-treatment visits at 30 (+3) and 90 (+7) days after the last dose of study drug, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks). For those patients in the survival follow-up who have not progressed at the time of study drug discontinuation, tumor assessments, including all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

l2: Brain scans with contrast (by CT or MRI) to be obtained with tumor assessment at screening (within 28 days of dosing). Patients without the presence of brain metastases at screening should also have a brain scan at the end of the induction part. Patients with brain metastases at screening should have brain scans with every scheduled tumor assessment.

m Archived tumor samples should be available for banking for assessment of relevant DNA, ribonucleic acid (RNA), and protein markers, such as PD-L1 or those involved in the CDK4/6 pathway. Tumor samples may be banked for up to 10 years.

n Trilaciclib or placebo will be administered as an IV infusion in 250 mL of D5W or sodium chloride solution 0.9% over approximately 30 minutes prior to E/P chemotherapy on Days 1 to 3 of every induction cycle. If there is any volume remaining in the trilaciclib or placebo infusion bag at the end of the 30 minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. The interval between doses of trilaciclib or placebo on successive days should not be greater than 28 hours. The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours. Trilaciclib or placebo will only be administered with chemotherapy. If administration of E/P chemotherapy is discontinued, trilaciclib or placebo should also be discontinued. Chemotherapy cannot be administered until after completion of the trilaciclib or placebo infusion. If the second or third dose of trilaciclib in any given cycle is not administered for any reason, do not administer the dose of etoposide or carboplatin chemotherapy on that day. After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, [redacted]; CBC assessment on Day 22; the Post-Treatment Visits; and the Survival Follow-up Phase of the study.

o During the induction part, atezolizumab should be administered following the administration of trilaciclib or placebo, etoposide, and carboplatin.

p Patient-reported outcomes should be completed at Days 1 of each cycle and at the post-treatment visits at 30 (+3) and 90 (+7) days after the last dose of study drug. [redacted]

q At least 5 patients enrolled in each treatment group will have trilaciclib, etoposide, and carboplatin PK samples collected on Day 1 of Induction Cycles 1 and 3 at the time points specified.

r Blood samples will be collected from all patients predose and 30 minutes after the end of atezolizumab infusion to determine the minimum and maximum observed serum atezolizumab concentration on Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 (+3) and 90 (+7) days after the last dose of study drug.

s Peripheral blood samples will be collected at predose on Day 1 of Induction Cycle 1, Day 1 of Maintenance Cycle 1 (first cycle of maintenance part), Day 1 of Maintenance Cycle 5, and at the post-treatment visit at 90 (+7) days after the last dose of study drug.

t Anti-atezolizumab therapeutic antibodies will be measured predose on Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 (+3) and 90 (+7) days after the last dose of study drug.

u Adverse events will be recorded from the time of informed consent. AEs will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug. All AEs should be followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

10. SCHEDULE OF STUDY PROCEDURES

Study procedures are summarized across all study visits within the schedule of assessments (Table 9-1).

10.1. Screening

Patients should be screened no more than 14 days before the first dose of study treatment is administered. Written informed consent must be obtained from each patient before the initiation of any screening procedures. Informed consent and brain scans may be obtained up to 28 days prior to the first study treatment administration. After a patient has given informed consent, eligibility will be determined by a review of the inclusion/exclusion criteria and completion of all screening procedures outlined in Table 9-1 and listed below.

- Collection of demographics
- Collection of medical history
- ECOG performance status evaluation
- Physical examination
- Height, weight, and vital signs measurements
- ECG
- Clinical chemistry, hematology, and urinalysis tests
- Thyroid-stimulating hormone (TSH), free thyroxine (T4), and free tri-iodothyronine (T3) tests
- Tumor assessment (by CT scan or MRI; see details in Section 11.1.1); CT or MRI scans obtained prior to informed consent will not need to be repeated if performed within 14 days prior to dosing.
- Brain scan with contrast (by MRI or CT); brain MRI or CT scans obtained prior to informed consent will not need to be repeated if performed within 28 days prior to dosing.

Monitoring of AEs and concomitant medications will commence at the time of informed consent. AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

10.2. Enrollment

Eligibility will be determined prior to enrollment, randomization, and the start of study treatment. Females of childbearing potential will have a serum pregnancy test. Eligible patients will be instructed on all protocol requirements, including any restrictions on concomitant medication usage.

Randomization will be performed within 3 days of the first dose of trilaciclib or placebo + E/P/A therapy, following confirmation that the patient is eligible for the study. Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part.

Archived tumor samples should be available for banking for assessment of relevant DNA, RNA, and protein markers, such as PD-L1 or those involved in the CDK4/6 pathway. Tumor samples may be banked for up to 10 years. For additional guidance regarding the shipment of samples to the central pathology laboratory, please refer to the Laboratory Manual.

10.3. Induction Part of the Study

10.3.1. Induction Cycle 1

Adverse events and concomitant medications will be monitored throughout the study. AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

Induction Cycle Day 1

Enrolled patients will return to the study center on study Day 1. The following procedures will be performed and results reviewed before study drug administration:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests (note: clinical chemistry and urinalysis tests may be obtained up to 72 hours prior to the first dose of each cycle of study treatments, and hematology tests may be obtained up to 24 hours prior to the first dose of each cycle of study treatments). The clinical chemistry and hematology results should be reviewed before dosing.
- [redacted]
- Plasma PK samples (predose samples for measurement of trilaciclib, etoposide, and carboplatin concentrations for patients in the PK subgroup; and for measurement of atezolizumab concentrations for all patients)
- Immunologic marker blood sample collection (predose) (Cycle 1, only)
- [redacted]

The timing for critical assessments/procedures is outlined in Table 9-1.

Patients that still meet all of the eligibility criteria will begin treatment in Induction Cycle 1. The first dose of study treatments (trilaciclib or placebo + E/P/A therapy) will be administered (as described in Section 8.1) and all Day 1 postdose procedures outlined in Table 9-1 will be completed. Postdose assessments on Day 1 are as follows:

- Vital signs (obtained within 15 minutes before and after trilaciclib or placebo, etoposide, carboplatin, and atezolizumab infusions; only needed once between infusions; and after the last infusion on Days 1 and 3)

- Plasma PK samples (postdose samples for measurement of trilaciclib, etoposide, and carboplatin concentrations for patients in the PK subgroup; and for measurement of atezolizumab concentrations for all patients as described in Section 11.2)

Induction Cycle 1 Days 2, 3, 8, and 15

All procedures and assessments to be conducted during Induction Cycle 1 Days 2, 3, 8, and 15 are outlined in Table 9-1. The DMC may recommend decreasing the frequency of hematological evaluations based on accumulating data. The investigators and institutional review boards (IRBs) or Independent Ethics Committees (IECs) will be notified if the frequency is reduced.

On Day 2 of Induction Cycle 1, study treatments (trilaciclib or placebo + etoposide) will be administered (as described in Section 8.1).

On Day 3 of Induction Cycle 1, study treatments (trilaciclib or placebo + etoposide) will be administered (as described in Section 8.1). The following additional assessments will be performed:

- Vital signs (obtained within 15 minutes before and after trilaciclib or placebo and etoposide infusions; only needed once between infusions; and after the last infusion on Days 1 and 3)

10.3.2. Induction Cycle 2

Adverse events and concomitant medications will be monitored throughout the study. AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

Induction Cycle 2 Day 1

Patients will return to the study center on Induction Cycle 2 Day 1. The following procedures will be performed and results reviewed before study drug administration:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests (note: clinical chemistry and urinalysis tests may be obtained up to 72 hours prior to the first dose of each cycle of study treatments, and hematology tests may be obtained up to 24 hours prior to the first dose of each cycle of study treatments). The clinical chemistry and hematology results should be reviewed before dosing.
- TSH, free T4, and free T3 tests
- FACT-L and FACT-An Questionnaires
- Plasma PK sample (predose atezolizumab sample)
- [redacted])

Vital signs should be obtained within 15 minutes before and after trilaciclib or placebo, etoposide, and carboplatin infusions; only once between infusions; and after the last infusion on Days 1 and 3.

In order to start Induction Cycle 2 as scheduled, on Day 1 of the cycle, patients must have an ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be ≤ Grade 1 or have returned to baseline. Dose modifications based on lack of recovery to these absolute neutrophil and platelet counts on the first day of treatment for Cycle 2 are outlined in Table 8-2. A delay of up to 9 weeks is permitted to allow recovery from any toxicity related to trilaciclib or placebo, carboplatin, or etoposide in order to meet the continuation criteria. A delay of up to 15 weeks is permitted to allow recovery and management from immune-related toxicities attributed to atezolizumab (12 weeks for recovery to ≤ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to ≤ 10 mg/day). If the patient meets the criteria for starting the subsequent cycle as stated in protocol Section 6.1.1, a delay of up to 2 weeks is permitted for administrative reasons (eg, holiday, vacation, etc.); however, a total delay of more than 9 weeks for trilaciclib or placebo + E/P, or 15 weeks for atezolizumab must be discussed with the medical monitor. If a cycle is delayed, the patient should still complete the clinical laboratory assessments and the FACT-L and FACT-An questionnaires on the scheduled Day 1 of the next cycle, as well as the actual first dosing day of the next cycle of trilaciclib or placebo + E/P/A chemotherapy.

A delay of > 9 weeks for recovery from any toxicity related to trilaciclib or placebo + E/P in order to meet the continuation criteria will result in discontinuation of trilaciclib or placebo + E/P. A delay of > 15 weeks for recovery and management of immune-related toxicities attributed to atezolizumab (12 weeks for recovery to ≤ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to ≤ 10 mg/day) will result in discontinuation of atezolizumab (see Section 8.4.5.3).

For patients who are eligible to initiate Induction Cycle 2, study treatments (trilaciclib or placebo + etoposide + carboplatin + atezolizumab) will be administered as described in Section 8.1.

Postdose assessments on Induction Cycle 2 Day 1 are as follows:

- Vital signs (obtained within 15 minutes before and after trilaciclib or placebo, etoposide, carboplatin, and atezolizumab infusions; only needed once between infusions; and after the last infusion on Days 1 and 3)
- Plasma PK sample (postdose sample for measurement of atezolizumab concentration as described in Section 11.2, for all patients)

Induction Cycle 2 Days 2, 3, 8, and 15

All procedures and assessments to be conducted during Induction Cycle 2 Days 2, 3, 8, and 15 are outlined in Table 9-1. The DMC may recommend decreasing the frequency of hematological evaluations based on accumulating data. The investigators and IRBs will be notified if the frequency is reduced.

On Day 2 of Induction Cycle 2, study treatments (trilaciclib or placebo + etoposide) will be administered (as described in Section 8.1).

On Day 3 of Induction Cycle 2, study treatments (trilaciclib or placebo + etoposide) will be administered (as described in Section 8.1). The following additional assessments will be performed:

- Vital signs (obtained within 15 minutes before and after trilaciclib or placebo, etoposide, and atezolizumab infusions; only needed once between infusions; and after the last infusion on Days 1 and 3)

For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle for the first 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter, until the occurrence of disease progression. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments.

10.3.3. Induction Cycles 3 and 4

Procedures and assessments to be performed during Induction Cycle 3 are similar to Induction Cycle 1 (see Section 10.3.1 and Table 9-1).

Procedures and assessments to be performed during Induction Cycle 4 are similar to Induction Cycle 2 (see Section 10.3.2 and Table 9-1).

In order to start Induction Cycles 3 and 4 as scheduled, on Day 1 of the cycle, patients must have an ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline. Dose modifications based on lack of recovery to these absolute neutrophil and platelet counts on the first day of treatment for Cycle 2 are outlined in Table 8-2. A delay of up to 9 weeks is permitted to allow recovery from any toxicity related to trilaciclib or placebo, carboplatin, or etoposide in order to meet the continuation criteria. A delay of up to 15 weeks is permitted to allow recovery and management from immune-related toxicities attributed to atezolizumab (12 weeks for recovery to $\leq$ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to $\leq$ 10 mg/day). If the patient meets the criteria for starting the subsequent cycle as stated in protocol Section 6.1.1, a delay of up to 2 weeks is permitted for administrative reasons (eg, holiday, vacation, etc.); however, a total delay of more than 9 weeks for trilaciclib or placebo + E/P, or 15 weeks for atezolizumab must be discussed with the medical monitor. If a cycle is delayed, the patient should still complete the clinical laboratory assessments and the FACT-L and FACT-An questionnaires on the scheduled Day 1 of the next cycle, as well as the actual first dosing day of the next cycle.

A delay of > 9 weeks for recovery from any toxicity related to trilaciclib or placebo + E/P in order to meet the continuation criteria will result in discontinuation of trilaciclib or placebo + E/P. A delay of > 15 weeks for recovery and management of immune-related toxicities

attributed to atezolizumab (12 weeks for recovery to ≤ Grade 1 and up to an additional 3 weeks for steroid taper of oral prednisone or equivalent to ≤ 10 mg/day) will result in discontinuation of atezolizumab (see Section 8.4.5.3).

10.3.4. Atezolizumab Administration While Trilaciclib or Placebo + E/P Is Held

During the induction part, interruption or delay of trilaciclib or placebo + E/P does not preclude continuation of atezolizumab and vice versa. If the AE is immune related and attributed to atezolizumab, then trilaciclib or placebo + E/P will be continued for up to 4 cycles while atezolizumab is held. If an AE is attributed to trilaciclib or placebo, etoposide, or carboplatin (eg, hematologic toxicity) during the induction part of the study, then atezolizumab will be continued every 21 days while trilaciclib or placebo + E/P are held. During the period in which trilaciclib or placebo + E/P are held and atezolizumab is continued, patients should be monitored as follows prior to administering atezolizumab every 21 days:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests (note: clinical chemistry and urinalysis tests may be obtained up to 72 hours prior to the first dose of each cycle of study treatments, and hematology tests may be obtained up to 24 hours prior to the first dose of each cycle of study treatments). The clinical chemistry and hematology results should be reviewed before dosing.
- FACT-L and FACT-An Questionnaires

10.4. Last Induction Cycle – Day 22

On Day 22 of the last induction cycle, patients will return to the clinic for ECG assessment and collection of a blood sample for hematology tests.

- If the patient continues directly into maintenance without interruption, then the hematology and ECG assessments will be performed as part of the Day 1 assessments in the first cycle of atezolizumab maintenance.

- If atezolizumab is held or discontinued for any reason after the last cycle of trilaciclib/placebo with carboplatin and etoposide, the patient should return to the clinic at the end (eg, Day 22) of this last induction cycle for hematology and ECG assessments.

Adverse events and concomitant medications will be monitored throughout the study. AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

For patients who have a confirmed CR, it is strongly recommended that they receive PCI after completion of chemotherapy. Patients with a confirmed partial response should also consider PCI after completion of chemotherapy based on the investigator's judgment.

10.5. Maintenance Part of the Study

Following induction, patients will proceed to the maintenance part of the study and receive atezolizumab every 21 days. Treatment in the maintenance part of the study will continue until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit.

10.5.1. Maintenance Cycle 1 and Odd Cycles

Adverse events and concomitant medications will be monitored throughout the study. AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

Maintenance Cycle 1 and Odd Cycles – Day 1

Patients will return to the study center on study Day 1 of Maintenance Cycle 1 and odd cycles in the maintenance part of the study. The following procedures will be performed and results reviewed before study drug administration:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests (note: clinical chemistry and urinalysis tests may be obtained up to 72 hours prior to the first dose of each cycle of study treatments, and hematology tests may be obtained up to 24 hours prior to the first dose of each cycle of study treatments). The clinical chemistry and hematology results should be reviewed before dosing.
- FACT-L and FACT-An Questionnaires
- Immunologic marker blood sample collection (predose) (Cycle 1 and 5, only)

The timing for critical assessments/procedures is outlined in Table 9-1.

For patients who continue to meet the continuation criteria as described in Section 6.1.1, atezolizumab will be administered (as described in Section 8.1) and all Day 1 postdose procedures outlined in Table 9-1 will be completed. Postdose assessments on Day 1 are as follows:

- Vital signs (obtained within 15 minutes before and after atezolizumab infusion)

10.5.2. Maintenance Cycle 2 and Even Cycles

Adverse events and concomitant medications will be monitored throughout the study. AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

Maintenance Cycle 2 and Even Cycles – Day 1

Patients will return to the study center on study Day 1 of Maintenance Cycle 2 and even cycles in the maintenance part of the study. The following procedures will be performed and results reviewed before study drug administration:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests (note: clinical chemistry and urinalysis tests may be obtained up to 72 hours prior to the first dose of each cycle of study treatments, and hematology tests may be obtained up to 24 hours prior to the first dose of each cycle of study treatments). The clinical chemistry and hematology results should be reviewed before dosing.
- TSH, free T4, and free T3 tests
- Tumor assessment (by CT scan or MRI after every even cycle for the first 9 months of the study [ie, approximately every 6 weeks] and after every third cycle [ie, approximately every 9 weeks] thereafter while receiving study drug; see details in Section 11.1.1)
- [redacted]
- Plasma PK sample (predose sample for measurement of atezolizumab concentration) (Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter)
- [redacted]

The timing for critical assessments/procedures is outlined in Table 9-1.

For patients who continue to meet the continuation criteria as described in Section 6.1.1, atezolizumab will be administered (as described in Section 8.1) and all Day 1 postdose procedures outlined in Table 9-1 will be completed. Postdose assessments on Day 1 are as follows:

- Vital signs (obtained within 15 minutes before and after atezolizumab infusion)
- Plasma PK samples (postdose sample for measurement of atezolizumab concentration as described in Section 11.2) (Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter)

10.6. Post-Treatment Visits

Patients will return to the study center for post-treatment visits at 30 (+3) days and at 90 (+7) days after the last dose of study drug. The following procedures will be performed at these visits:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests
- TSH, free T4, and free T3 tests

- Pregnancy test
- Tumor assessment (obtain tumor assessment by CT scan or MRI for patients who have not progressed at the time of study drug discontinuation [every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion]; see details in Section 11.1.1) after every even cycle for the first 9 months of the study and after every third cycle thereafter
- Brain scan with contrast (obtain brain scans by MRI or CT for patients who have not progressed at the time of study drug discontinuation [may be performed within 4 weeks])
- [redacted]
- Plasma PK sample for measurement of atezolizumab concentration (30 [+3] and 90 [+7] days after the last dose of study drug)
- [redacted]
- Immunologic markers blood sample collection (90 [+7] days after the last dose of study drug, only)

AEs and concomitant medications will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

After completing the post-treatment visits, patients will enter the long-term Survival Follow-up Phase.

10.7. Survival Follow-up Phase

Monthly phone calls will be made to each patient that is in the long-term Survival Follow-up Phase. Patients will be followed for survival at a minimum until 70% of the patients randomized to the study have died. In addition, for patients who have not had disease progression at the time of study drug discontinuation, tumor assessments, including all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

The following information will be collected monthly for all patients:

- Survival status
- Details of any anticancer treatment

10.8. Study Drug Discontinuation

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, [redacted] CBC assessment on Day 22; the Post-Treatment Visits; and the Survival Follow-up Phase of the study, which is to continue until at least 70% of randomized patients have died. Any abnormal results that are believed to be related to the study drug treatment should be repeated as often as deemed appropriate by the investigator until the abnormality resolves, returns to predose levels, or is otherwise explained.

10.9. Unscheduled Visits

Additional visits can be performed as appropriate and at the discretion of the investigator.

11. STUDY ASSESSMENTS

11.1. Tumor Response

Efficacy evaluation will be based on tumor response using RECIST v1.1, including objective response rate (ORR), PFS, and OS. Additionally, tumor response and immune-related progression-free survival (irPFS) will be assessed using irRECIST.

11.1.1. Tumor Assessments

For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle for the first 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug, until the occurrence of disease progression (see Table 9-1). CT or MRI scans obtained prior to informed consent will not need to be repeated if performed within 14 days prior to dosing. Brain scans performed as standard of care prior to informed consent will not need to be repeated if performed within 28 days prior to dosing. Assessments should be performed within 7 days prior to starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. For patients who have a confirmed CR, it is strongly recommended that they receive PCI after completion of chemotherapy. Patients with a confirmed PR should also consider PCI after completion of chemotherapy based on the investigator's judgment (see Section 8.8). Following the completion of the induction part, PCI may be administered concurrently with atezolizumab during the maintenance part. For those patients who have not progressed at the time of study drug discontinuation, tumor assessments, including all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

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

Investigators should follow the RECIST v1.1 guidelines (Eisenhauer 2009) for tumor assessments.

11.1.2. Tumor Lesions: Identification and Follow-up

11.1.2.1. Measurable Lesions

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

- 10 mm by CT or MRI (with a scan slice thickness of no greater than 5 mm)

Measurable lymph nodes must be ≥ 15 mm on the short axis by CT or MRI (with a scan slice thickness of no greater than 5 mm); only the short axis is to be measured at 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 that will be followed to quantitate the status of disease during the study. Lesions with the longest diameter, that are representative of all involved organs, and for which reproducible repeated measurements can be obtained should be selected as the target lesions.

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

11.1.2.2. Nonmeasurable Lesions

Nonmeasurable lesions include tumor lesions with a longest diameter < 10 mm, lymph nodes with ≥ 10 to < 15 mm short axis, or nonmeasurable lesions such as leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by CT scan or MRI (Eisenhauer 2009).

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.

11.1.2.3. New Lesions

Any new lesions should be identified and recorded at each follow-up assessment, as these are markers of disease progression. As defined in the RECIST v1.1 guidelines (Eisenhauer 2009), new lesions include the following:

- A lesion in an anatomical location that was not scanned at baseline

- Equivocal new lesion of small size that with continued therapy and follow-up is found to progress and represent new disease (progression should be considered as of the date of the initial scan)
- Negative positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG-PET) at baseline, but has a positive FDG-PET at follow-up
- No FDG-PET at baseline and a positive FDG-PET at follow-up that corresponds to a new site of disease as confirmed by CT (date of disease progression should be the date of the initial abnormal FDG-PET scan)

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

11.1.3. Definitions of Tumor Response and Disease Progression

The determination of SCLC tumor response and progression will be based on the RECIST v1.1 criteria (Eisenhauer 2009). The definitions for tumor response per the RECIST v1.1 criteria are as follows:

11.1.3.1. Evaluation of Target Lesion Response

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

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

11.1.3.2. Evaluation of Nontarget Lesions

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

11.1.3.3. Evaluation of Overall Response

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

Table 11-1 describes the evaluation of overall response at each time point based on target and nontarget lesion responses at each time point, as well as the appearance of new lesions. The best overall response is the best response recorded from the start of the treatment until disease progression. Confirmation of CR and PR is required as described in Sections 11.1.3.1 and 11.1.3.2.

Table 11-1 Evaluation of Overall Response at Each Time Point

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

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

11.1.4. Treatment Beyond Disease Progression Per RECIST Version 1.1

Evidence indicates some patients treated with immunotherapy may derive clinical benefit after initial evidence of apparent disease progression (Wolchok et al 2013; Nishino 2013). Therefore, study drug administration may be continued until loss of clinical benefit, provided the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient to continue and the patient has provided re-consent. Study drug administration refers to trilaciclib or placebo + E/P/A during the induction part or atezolizumab during the maintenance part. Treatment past disease progression per RECIST v1.1 should only be considered if a patient is clinically stable and has the following:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values; eg, new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- All patients continuing treatment beyond progression must sign a separate written consent to acknowledge deferring alternative potential treatment options in favor of continuing study treatment at the time of initial apparent progression.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. Decisions to

continue treatment beyond initial progression per RECIST v1.1 may be discussed with the medical monitor and should be documented in the study records.

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

Immune-related disease progression (irPD) must be confirmed with worsening of disease bulk on the next tumor assessment, performed at least 4 weeks after the disease progression by RECIST v 1.1 was first noted. If the criteria of worsening disease bulk are met on 2 consecutive scans, the patient is determined to have confirmed irPD. If following an initial progression, the patient has a subsequent immune-related response (immune-related CR, PR or SD; determined from baseline), then the original progression is not confirmed and the patient may continue to receive study treatment and any subsequent progression must be confirmed on the next consecutive tumor assessment.

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

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST v1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event. For patients who continue on treatment beyond RECIST v1.1-defined progression and have confirmed irPD, the date of the previous irPD will be recorded as the irPFS date.

11.2. Pharmacokinetic Assessments

In a subgroup of at least 5 patients in each treatment group of the study, blood samples will be collected for the measurement of trilaciclib, etoposide, and carboplatin concentrations in plasma at the time points outlined below and in Table 9-1. The sites identified to participate in the trilaciclib, etoposide, and carboplatin PK substudy will be based on the site's ability to complete all PK assessments. Sites will be identified during the site selection process. All patients in each treatment group will have blood samples collected for the measurement of atezolizumab plasma concentrations. Comprehensive information on blood sample acquisition, the specific type of collection tube with anticoagulant, and handling and storage are to be found in the Laboratory Manual. The analytical laboratory will measure plasma concentrations of trilaciclib, etoposide, carboplatin, and atezolizumab using validated

methods. Any remaining samples may be stored long term (up to 10 years) for the future analysis of trilaciclib drug metabolites.

Day 1 of Induction Cycles 1 and 3

Blood samples will be collected at the following time points on Day 1 of Induction Cycles 1 and 3 for all patients enrolled in the PK subgroup of the study: predose (0 hour; prior to dosing of trilaciclib or placebo) and at 0.5 (end of infusion [EOI] of trilaciclib or placebo), 1 (EOI of carboplatin), 2 (EOI of etoposide), 4, 6, and 24 (prior to trilaciclib or placebo dose on Day 2) hours. The EOI sample for trilaciclib or placebo should be drawn 2 to 5 minutes prior to the EOI. The EOI samples for trilaciclib or placebo, carboplatin, and etoposide must be drawn after completing infusion of the drugs and the actual times at which the samples were drawn should be documented. A ± 5-minute time window will be allowed for samples collected between the following time points: predose to 2 hours after the end of trilaciclib or placebo infusion. A ± 10-minute time window will be allowed for samples collected between the following time points: 4 to 6 hours after the end of trilaciclib or placebo infusion. A ± 1-hour time window will be allowed for the 24-hour time point. The actual time of blood sample collection should be documented in the eCRF. The Induction Cycle 1 Day 1 sampling scheme is summarized in Table 11-2.

Table 11-2 Day 1 of Induction Cycles 1 and 3 Blood Sampling Scheme Based on Predicted Administration Times of Trilaciclib/Placebo, Carboplatin, and Etoposide

Sample	1	2	3	4	5	6	7
Sample Time (h) from start of trilaciclib/ placebo infusion	0 (Predose[a])	0.5[b] (Trilaciclib /Placebo EOI[c])	1.0 (Carbo EOI[c])	2.0 (Etop EOI[c])	4.0[d]	6.0[e]	24[f] (prior to trilaciclib dose on Day 2)

Carbo = carboplatin; EOI = end of infusion; Etop = etoposide; h = hour

Times are approximate. For simplicity, assumptions were based on 0.5 hour infusion of trilaciclib/placebo. Actual times will be recorded and may vary from those listed here.

a Predose is defined as prior to initiation of trilaciclib/placebo administration.

b The EOI sample for trilaciclib should be drawn 2 to 5 minutes prior to the EOI.

c Trilaciclib/placebo – 30-minute infusion; carboplatin infusion = 30 minutes; etoposide infusion = 60 minutes

d Sample #5 to be collected 4 hours from the start of trilaciclib/placebo infusion (eg, 3.5 hours from trilaciclib/placebo EOI)

e Sample #6 to be collected 5 hours from the start of trilaciclib/placebo infusion (eg, 4.5 hours from trilaciclib/placebo EOI)

f Sample #7 to be collected prior to initiation of trilaciclib/placebo Day 2 dose

If it is necessary to slow the infusion rate of any of the study drugs at a given visit for a particular patient, the collection time of any subsequent PK sample(s) should be adjusted accordingly to ensure that the sample is collected at the actual EOI (trilaciclib/placebo, carboplatin, and/or etoposide). Please continue to use the sample labels with the scheduled time; however, ensure that actual time of sample collection is recorded appropriately on the eCRF.

Day 1 of Induction Cycles 1, 2, 3, and 4; Maintenance Cycles 4, 8, 12, and Every Eighth Cycle Thereafter; and at 30 and 90 Days After the Last Dose of Study Drug

Blood samples will be collected at the following time points relative to atezolizumab infusion to determine the minimum and maximum observed serum atezolizumab concentration: predose and 30 minutes after the end of the atezolizumab infusion.

Pharmacokinetic Parameters

Pharmacokinetic parameters to be derived from trilaciclib, etoposide, carboplatin, and atezolizumab plasma concentration-time data are presented in Table 11-3.

Table 11-3 Pharmacokinetic Parameters

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

Pharmacokinetic samples may also be obtained from additional patients depending on the outcome of initial PK analysis.

[redacted]

11.4. Safety Assessments

Safety evaluations will be conducted at baseline and throughout the study. Safety will be assessed by evaluation of AEs, physical examinations, vital sign measurements, ECGs, clinical laboratory data, and IRRs. The following information will also be evaluated as part of the safety assessment: kinetics of changes in CBCs; hematologic toxicities, including febrile neutropenia and infections; red blood cell (RBC) and platelet transfusions; hematopoietic growth factor utilization; systemic antibiotic use; and chemotherapy dose reductions and dose interruptions and atezolizumab dose interruptions.

The toxicity of trilaciclib administered IV with chemotherapy will be assessed by the investigators using the NCI CTCAE, Version 4.03.

11.4.1. Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

11.4.1.1. Definition of Adverse Event

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

An abnormal laboratory value is not an AE unless it is considered to be clinically significant.

Adverse events include the following:

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

An AE does not include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure will be an AE
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms
- Disease progression

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

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

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

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

11.4.1.2. Definition of Serious Adverse Event

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

- Results in death
- Is life threatening
  NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting (see Section 11.4.1.10) is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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

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

11.4.1.3. Definition of Adverse Events of Special Interest

Adverse events of special interest for atezolizumab are defined in Appendix 3.

11.4.1.4. Assessment of the Severity of Adverse Events

The severity (toxicity grade) of AEs will be graded according to the NCI CTCAE, Version 4.03 (see Appendix 5).

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

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

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

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

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

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

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

11.4.1.6. Assessment of the Outcome of Adverse Events

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

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

The outcome will be assessed according to the following:

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

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

Safety surveillance reporting of AEs commences at the time of informed consent. AEs will be collected through 30 days after the last dose of study drug; SAEs and AESI will be collected through 90 days after the last dose of study drug.

11.4.1.8. Documentation of Adverse Events and Serious Adverse Events

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

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

- A description of the AE in medical terms, not as reported by the patient. Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”).

- Date of onset (start date)
- Date of recovery (stop date)
- Grade as assessed by the investigator according to the definitions in the AE Grading Scale. If the AE is not specifically listed in Appendix 1, use the following grades:
  Grade 1 mild
  Grade 2 moderate
  Grade 3 severe
  Grade 4 life-threatening or disabling
  Grade 5 death

11.4.1.9. Adverse Event Coding

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

11.4.1.10. Reporting of Serious Adverse Events and Adverse Events of Special Interest

The reporting period for SAEs and AESI (see Appendix 3) begins from the time of informed consent through 90 days after the last dose of study treatment (safety follow-up phone call). Any SAE that is thought to be related to the study drug or any AESI that occurs after the reporting period must be reported **within 24 hours** of discovery of the SAE or AESI.

All SAEs and AESI must be entered into the eCRF and the initial SAE or AESI form should be completed and sent to the safety team within 24 hours of first knowledge of the event by the study personnel.

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

11.4.1.11. Follow-up of Adverse Events

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

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

Prior to the conclusion of the study at the site, the investigator should notify the medical monitor of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to the study drug.

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

11.4.1.12. Regulatory Aspects of Adverse Event Reporting

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

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

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

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

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

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

G1 Therapeutics, or their designee, and their collaborators are responsible for submitting reports of AEs associated with the use of the study drug that are both serious and unexpected to the FDA and European National Competent Authorities, the Medicine Evaluation Board,

and the Competent Authorities in other Member States, if applicable, in an expedited time frame in compliance with current legislation. Unexpected SAEs that are already reported to the European Medicines Agency Eudravigilance database do not have to be reported again to the relevant authorities. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC.

The expedited reporting will occur no later than 15 calendar days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be a maximum of 7 calendar days for a preliminary report with another 8 days for completion of the final report. The investigator is encouraged to discuss with the medical monitor any adverse experiences for which the issue of reportability is unclear or questioned.

11.4.1.13. Handling of Overdoses and Toxicity

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

11.4.1.14. Reporting of Pregnancies

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

Each pregnancy in a study patient or partner of a study patient must be reported to the sponsor within 24 hours of learning of its occurrence. If a patient becomes pregnant, study drug administration must be discontinued immediately. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

No information is currently available regarding the effects of trilaciclib on fertility, gestation, or subsequent child development.

Atezolizumab can cause fetal harm when administered during pregnancy. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

The avoidance of pregnancy or fathering a child (including sperm donation) is suggested for 6 months following the discontinuation of study drug.

11.4.2. **Clinical Laboratory Assessments**

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

- Hematology (hemoglobin, WBCs with differential and platelet counts)

- Chemistry (albumin, alkaline phosphatase [ALP], total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, LDH, amylase, lipase, sodium, and BUN)
- TSH, free T4, and free T3
- Urinalysis (semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin; and a microscopic examination, including RBC, WBC, and casts will be performed, if necessary)

If the subsequent cycle is delayed, the patient should still complete the clinical laboratory assessments on the scheduled Day 1, as well as on the actual first dosing day of the next cycle.

Laboratory parameters will be analyzed by a local certified laboratory and a report of the laboratory values will be sent to the study center. 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 will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality, or it is deemed that recovery is not feasible.

Laboratory toxicities will be assessed using the NCI CTCAE, Version 4.03 (see Appendix 5).

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

11.4.3. Demographics and Vital Signs

The following will be collected:

- Height in centimeters (cm)
- Body weight in kilogram (kg)
- Body temperature (Celsius)
- Systolic and diastolic blood pressure, pulse rate, respiration rate, and pulse oximetry will be measured with the patient. Blood pressure should be assessed after 5 minutes of rest.

11.4.4. Physical Examination

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

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

11.4.5. Electrocardiogram Assessments

Standard 12-lead ECGs will be performed as outlined in Table 9-1. Patients should rest for 5 minutes prior to each ECG assessment.

Any ECG with a QTc value of > 500 should be repeated every 5 minutes for a total of 3 ECGs to confirm this finding. The QTc value should also be confirmed via manual read.

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

11.4.6. Concomitant Medications

Review of concomitant medications will occur at the times outlined in Table 9-1. See Section 8.6 for more information on concomitant medications.

11.5. Patient Reported Outcomes

The FACT-L and FACT-An instruments will be administered to the patients by a designated trained study site staff member. The instruments will be administered in the clinic for the baseline assessment (on or within 1 day prior to initiation of study treatment), at Day 1 of each cycle, and at the Post-Treatment visit. If the subsequent cycle is delayed, the patient should still complete the PRO on the scheduled Day 1, as well as on the actual first dosing day of the next cycle. Where possible, the same staff member will administer the instrument at each site.

Both the FACT-L and FACT-An contain a core general questionnaire that measures physical, social/family, emotional, and functional well-being. The FACT-L has an additional lung cancer subscale (FACT-L) (Cella 1995). The FACT-An has an additional subscale that measures the impact of fatigue and other anemia-related symptoms on patients with cancer (FACT-An) (Yellen 1997). The core general questionnaire is the same for both instruments; as such, at each assessment, the core questionnaire will be administered once along with the lung and anemia subscales.

11.6. Immunologic Markers

The addition of trilaciclib to standard chemotherapy could provide clinical benefit to patients with CDK4/6-independent cancers through the reduction of myelosuppression-related side effects and improved chemotherapy activity. There are at least 2 potential mechanisms by which trilaciclib may improve chemotherapy activity: maintaining dose intensity and maintaining immune system function through repeated cycles of chemotherapy. In addition to the common side effects that result from myelosuppression, chemotherapy-induced immunosuppression may limit response rates and survival due to an inability of the damaged host immune system to effectively mount a response against the cancer. The impact of chemotherapy on the host immune system has been shown to be a double-edged sword, where the specific chemotherapeutic agent and dosing regimen (low dose versus standard dosing) dictate the impact on the immune system. Chemotherapeutic agents may elicit part of their antitumor 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. Preclinical mouse models have shown that chemotherapeutic response is more robust in tumors transplanted into immunocompetent mice compared to immunodeficient mice, suggesting that the loss of immune system function is detrimental to the overall efficacy of the chemotherapy (Apetoh 2007; Casares 2005). In support of these data, severe lymphopenia (< 1000 cells/µL) in patients with breast cancer, advanced soft tissue sarcoma, and non-Hodgkin lymphoma has been shown to negatively affect PFS and OS (Ray-Coquard 2009).

Since immune reprogramming is now believed to be an important mechanism of chemotherapy response, therapeutic approaches to maintain bone marrow health and immune system function should enhance this activity. The effect of trilaciclib in combination with chemotherapy and a checkpoint inhibitor was evaluated in MC38 tumor-bearing mice treated with trilaciclib, oxaliplatin, or anti-PD-L1 alone or in combination. Tumor size was measured during and post treatment for 100 days. The addition of trilaciclib to an oxaliplatin/ anti-PD-L1 combination (TOP) treatment significantly improved the overall response rate, complete response rate, and median OS compared to oxaliplatin/anti-PD-L1 combination (93% vs 46%; 79% vs 38%; not reached at 100 days vs 59 days, respectively). Taken together, this demonstrates that trilaciclib, which has been shown to preserve immune function during chemotherapy, enhances the antitumor activity of chemotherapy/anti-PD-L1 combination therapy.

Therefore, to evaluate the impact of trilaciclib administration on chemotherapy-induced changes of the immune system, peripheral blood immune subsets will be characterized in patients enrolled into the study. Immunophenotypic changes will be compared between patients receiving E/P/A therapy plus placebo or trilaciclib. To assess these changes, peripheral blood will be collected at predose on Day 1 of Induction Cycle 1, Day 1 of Maintenance Cycle 1 (first cycle of maintenance part), Day 1 of Maintenance Cycle 5, and at the post-treatment visit at 90 (+7) days after the last dose of study drug.

11.7. Appropriateness of Measurements

The measures of efficacy, PK, and safety evaluated in this study are based on the mechanism and activity of trilaciclib, standard types of assessments typically performed in patients with SCLC, and prior clinical observations derived from patients receiving trilaciclib + E/P/A therapy. The measurement of tumor response based on the RECIST v1.1 (Eisenhauer 2009) is standard. The PK and safety measures included in this study are also standard.

12. STUDY TERMINATION OR STUDY DRUG DISCONTINUATION

12.1. Study Termination

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

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

12.2. Site Termination

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

12.3. Discontinuation of Study Drug

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

- A patient suffers an AE that, in the judgment of the investigator, sponsor, or medical monitor, presents an unacceptable risk to the patient (see Section 8.4.5)
- General or specific changes in the patient's condition (eg, a significant intercurrent illness or complication) that, in the judgment of the investigator, are unacceptable for further administration of study drug
- Occurrence of pregnancy
- Significant noncompliance with protocol requirements
- The sponsor or legal representative of the sponsor requests the patient to withdraw
- Patient has radiologically documented disease progression and the physician determines the patient is not deriving clinical benefit as defined in Section 11.1.4.

Discontinuation or interruption of trilaciclib or placebo + E/P does not preclude continuation of atezolizumab and vice versa. For instance, if an AE is attributed to trilaciclib or placebo, etoposide, or carboplatin (eg, hematologic toxicity) during the induction part; then atezolizumab will be continued while the trilaciclib or placebo + E/P are held. While the trilaciclib or placebo + E/P are held, the patient will continue to receive atezolizumab, be monitored for safety, and will begin the next trilaciclib or placebo + E/P/A-containing induction cycle after the toxicity resolves. If the AE is immune related and attributed to atezolizumab; then trilaciclib or placebo + E/P will be continued for up to 4 cycles while the atezolizumab is held.

After discontinuation of all study drugs, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, [redacted] CBC assessment on Day 22; all Post-Treatment Visits; and the Survival Follow-up Phase of the study. A patient who discontinues study treatment for reasons other than progressive disease will have a CT or MRI scan every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

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

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 CRF.

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

12.4. Withdrawal of Patients from the Study

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

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

All data collected prior to the date of withdrawal of consent will remain in the clinical database.

13. STATISTICS

Full details on the statistical analyses to be performed will be provided in separate statistical analysis plans (SAPs); due to discrepancies between regional regulatory requirements, details of the analyses will be specific to the endpoints in each region and will be defined in detail in the respective regional SAP prior to unblinding. Hence, details of the methods are not fully described in this protocol. For any differences in analyses between the protocol and SAP, the plan as outlined in the SAP will supersede the protocol.

While this Study G1T28-05 was originally designed to evaluate OS as the primary efficacy endpoint comparing trilaciclib + E/P/A to placebo + E/P/A, recent clinical results from Study G1T28-02 in patients with treatment-naive extensive-stage SCLC comparing trilaciclib plus E/P to placebo + E/P, provided compelling evidence that trilaciclib decreased myelosuppression across 3 lineages: neutrophils, RBC, and lymphocytes and achieved a meaningful level of myelopreservation. Critical hematologic myelosuppression endpoints were identified from that study and will be applied across the trilaciclib program. Hence, Study G1T28-05, where the chemotherapy backbone of etoposide and carboplatin and the patient population is the same as Study G1T28-02, is being modified to broaden the analysis of trilaciclib benefit to include multiple primary and key secondary endpoints related to myelosuppression, while retaining OS as a secondary endpoint. This amendment changes the primary endpoint of Study G1T28-05 from OS to primary and key secondary endpoints measuring clinically meaningful reductions in myelosuppression. This revision does not alter the ability of G1T28-05 to fulfill its original goal, but rather these changes facilitate the sponsor's ability to confirm the benefit of trilaciclib for treatment of myelosuppression in a second randomized, double-blinded, placebo-controlled study in first line SCLC. The same myelopreservation mechanism of action (MOA) of trilaciclib that is associated with improvement in myelosuppression is also hypothesized to potentially impact antitumor efficacy, such as OS. Therefore, changing the primary endpoint to myelosuppression allows for an earlier assessment of trilaciclib MOA and efficacy, with OS retained as a later manifestation of its effect. Although the primary endpoint for the G1T28-05 protocol was designed to be OS, the data collection for the myelosuppression analyses has been consistent with the data collection in the other trilaciclib clinical studies evaluating myelosuppression as a primary endpoint. As such, the data for this revised primary analysis has been collected throughout the study. This change in endpoints also does not alter the assessments or protocol-defined patient care.

At the time of performing the primary and secondary myelosuppression analyses, all patients will have completed the randomized induction treatment part of the study and will have discontinued trilaciclib or placebo. However, patients may still be in the atezolizumab monotherapy maintenance part of the study or being followed for survival. This will ensure that this amendment will not incur any potential operational bias for the PFS/OS analysis results.

13.1. Sample Size and Power

The initial sample size calculations were based on a primary endpoint of OS where a sample size of 100 (1:1 treatment allocation ratio between the two groups of placebo + E/P/A and

trilaciclib + E/P/A) provided 80% power to detect a hazard ratio of 0.6 using an overall type 1 error probability of 0.1 (1-sided). With the change in endpoints outlined in this amendment, the sample size calculation is now based on demonstrating the superiority of trilaciclib + E/P/A versus placebo + E/P/A with respect to at least one of the primary endpoints.

With this amendment, the overall type I error rate is now 0.025 (1-sided) and the type II error rate used to compute sample size is 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using the most conservative Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.025/2 = 0.0125 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation (StD) of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 2 days between the treatment groups (trilaciclib + E/P/A versus placebo + E/P/A) requires, 82 evaluable patients (41 per treatment arm). This implies that 88 patients need to be randomized assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for placebo + E/P/A, testing for an absolute reduction of 34% to 11% with trilaciclib + E/P/A would require a sample size of at least 100 patients (50 per treatment arm). Assuming a 95% evaluability rate, at least 106 patients need to be enrolled to complete the study. Therefore, the final adjusted sample size is 106 to account for the evaluation of 2 primary endpoints.

All calculations were carried out using the POWER procedure in SAS® version 9.4.

13.2. General Considerations

13.2.1. Analysis Sets

The intent-to-treat (ITT) analysis set includes all randomized patients. Analyses using the ITT will be conducted on the basis of the assigned treatment. All efficacy analyses will be assessed using the ITT and the ITT is the primary analysis set for analysis. A modified ITT (mITT) analysis set is a subset of the ITT analysis set and will only include the ITT patients who received at least 1 dose of study drug. Supportive sensitivity analyses will be conducted based on the mITT analysis set for primary and key secondary efficacy endpoints to evaluate the robustness of the results. Analyses using the mITT will be conducted on the basis of the assigned treatment.

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

A per-protocol (PP) analysis set is a subset of the mITT analysis set and may also be used to analyze select endpoints; it will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations, which will be fully defined and documented before unblinding. The criteria for inclusion in the PP analysis set will be finalized and documented prior to unblinding patients in the study.

The response evaluable analysis set will include all patients who are in the mITT and have at least 1 postbaseline tumor assessment, or have clinical progression as noted by the investigator before their first postbaseline tumor scan or have died due to disease progression before their first postbaseline tumor scan. The response evaluable analysis set will be used for analyses of tumor response.

The PK set will include all dosed patients in Part 1 with evaluable PK data.

13.2.2. **Timing of Analyses**

13.2.2.1. DMC Reviews

A DMC will monitor accumulating safety data according to a charter that defines its roles and responsibilities. The DMC will perform reviews after approximately 12 patients have been enrolled and have completed at least 1 cycle to assess the initial safety data from the 2 groups, and then approximately every 4 months during the Treatment Phase, depending upon the enrollment rate. Additional reviews may occur based on DMC requests. The committee will consist of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, SCLC) and biostatistics. These individuals will be entirely independent of the conduct of the study.

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

13.2.2.2. Final Analysis

The final analysis will be conducted after all patients have had the opportunity to receive at least 12 weeks of treatment (ie, randomized induction treatment part of the study). All study data collected through the time of the final analysis data cut, will be included in the final analysis. This includes, but is not limited to, the final myelosuppression analysis, final ORR analysis, and interim PFS/OS analyses.

At the time of the final analysis, the sponsor will be unblinded; however, investigators and patients will remain blinded.

13.2.2.3. End of Study Analysis

Patients will be followed for survival until at least 70% of the patients have died at which time an end of study analysis for OS and PFS will be done. Reported results, with the exception of the myelosuppression analyses, will be cumulative in nature, including all data collected during the entire study; the myelosuppression analyses will be complete at the final analysis and no additional data will be expected. Additional PFS/OS analyses may be done with the timing to occur between the first interim PFS/OS efficacy analysis and the end of study PFS/OS analysis.

13.2.3. **General Considerations for Data Analysis**

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

Data will be summarized descriptively by treatment group. Treatment differences between treatment groups will be calculated as trilaciclib + E/P/A therapy versus placebo + E/P/A therapy. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, and minimum and maximum values. The descriptive summaries of time-to-event data will include median, 25% and 75% percentiles, and standard error. All data will be listed for all patients. All CIs will be 95%, unless stated otherwise.

For the primary and key secondary endpoints, a multiple testing procedure will be used to control the overall familywise error rate at $\alpha = 0.025$ (one-sided) for the comparisons of trilaciclib + E/P/A to placebo + E/P/A (See Section 13.5.4).

All other statistical tests will be conducted at a 2-sided significance level of 0.05 unless otherwise specified (trilaciclib + E/P/A versus placebo + E/P/A). Where appropriate, model-based point estimates, together with their 95% CIs will be presented along with the 2-sided p-value for each test.

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

[redacted]

13.3. Baseline and Demographic Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment and overall.

13.4. Prior and Subsequent Anticancer Therapies

All prior and subsequent anticancer therapy verbatim terms will be coded to Anatomical Therapeutic Classification (ATC) and PT using the World Health Organization Drug Dictionary (WHO-DD Version Sep2017). The number and percentage of randomized patients receiving subsequent anticancer therapy will be provided by systemic anticancer therapy. All subsequent anticancer therapies will be presented in a patient listing.

13.5. Efficacy Analyses

Unless otherwise specified, all the myelosuppression efficacy analyses will be based on the ITT. Unless otherwise specified, all primary and key secondary efficacy endpoints will be evaluated and derived for the induction treatment period between the date of randomization and the end of the last cycle in the protocol-defined induction phase (ie, last cycle of placebo or trilaciclib plus E/P/A).

13.5.1. Primary Myelosuppression Efficacy Endpoints

The primary myelosuppression efficacy endpoints are defined as follows:

All Regions
Duration of severe (Grade 4) neutropenia in Cycle 1 Occurrence of severe (Grade 4) neutropenia

13.5.1.1. Methods of Analysis for Primary Myelosuppression Efficacy Endpoints

A 2-sided p-value will be calculated for the DSN in Cycle 1 using nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA will include study baseline ANC value as covariate, stratification factors of ECOG performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no), and treatment as a fixed effect. Along with the descriptive statistics, the Hodges-Lehmann estimate of median difference between the 2 treatment groups, together with its 95% CIs will be provided.

The occurrence of severe (Grade 4) neutropenia is a binary response variable (yes versus no) and will be analysed to compare trilaciclib and placebo using modified Poisson regression (Zou 2004) to account for the variable duration of the induction treatment period for each patient. The model will include baseline value as covariate, the stratification factors of ECOG performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no), and treatment as a fixed effect. The 1-sided p-value adjusted relative risk (aRR) (trilaciclib vs placebo) and its 95% CIs will be presented.

A detailed description of the analysis methods will be provided in the SAPs.

13.5.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are defined in the table below.

Region 1	Region 2
Occurrence of RBC transfusions on/after Week 5 (proportion of patients)	Overall survival (will not be factored into multiplicity adjustment)
Occurrence of G-CSF administration (proportion of patients)	All-cause dose reductions (number of events)
Composite MAHE composed of the following 5 components (number of events for all components): • All-cause hospitalizations • All-cause dose reductions • Febrile neutropenia • RBC transfusions on/after Week 5 • Prolonged severe (Grade 4) neutropenia (> 5 days)	Occurrence of RBC transfusions on/after Week 5 (proportion of patients)
	Occurrence of G-CSF administration (proportion of patients)

13.5.2.1. Methods of Analysis for OS

Although OS is a key secondary endpoint in Region 2, OS will be analyzed with a descriptive intention and will not be factored into multiplicity adjustment as described in Section 13.5.3. That is, no formal statistical testing will be planned. The analysis of OS will be primarily aimed at showing lack of harm from trilaciclib.

OS will be calculated as the time (months) from the date of randomization to the date of death due to any cause. Patients who do not die during the study will be censored at the date last known to be alive. Patients lacking data beyond the date of randomization will have their survival time censored at the date of randomization. OS will not be censored if a patient receives subsequent anticancer treatments after discontinuation of the study drugs.

13.5.2.2. Methods of Analysis for Key Secondary Myelosuppression Endpoints

A binary response variable (yes versus no) for the key secondary endpoints will be analyzed to compare trilaciclib and placebo using modified Poisson regression (Zou 2004) as outlined in Section 13.5.1.1.

The total number of MAHE will be analyzed to compare trilaciclib and placebo using a negative binomial regression model to account for the variable duration of the induction treatment period for each patient. The model includes stratification factors of ECOG performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no), and treatment as a fixed effect. The 1-sided p-value adjusted relative risk (aRR) (trilaciclib vs placebo) and its 95% CIs will be presented. The cumulative incidence of events will be presented graphically.

A more detailed description of the analysis methods will be provided in the SAPs.

13.5.3. Multiplicity Adjustment for the Primary and Key Secondary Myelosuppression Efficacy Endpoints

To accommodate the primary and key secondary myelosuppression efficacy endpoints, a Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the multiple null hypotheses in the strong sense at a 1-sided α=0.025 level. The one-sided p-values for these comparisons will be used for the multiple test procedure. The general testing strategy is described below for Region 1 (Section 13.5.3.1) and Region 2 (Section 13.5.3.2) with more detailed information provided in the respective SAPs.

13.5.3.1. Multiplicity Adjustments in Region 1

The multiplicity problem includes the following 10 hypotheses of no effect:

- Hypothesis H1. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H2. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of severe (Grade 4) neutropenia.

- Hypothesis H3. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of RBC transfusions on/after Week 5 on study.
- Hypothesis H4. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of G-CSF administration.
- Hypothesis H5. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for the MAHE composite.
- Hypothesis H6. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for all-cause hospitalizations in the MAHE composite.
- Hypothesis H7. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for all-cause dose reductions in the MAHE composite.
- Hypothesis H8. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for febrile neutropenia in the MAHE composite.
- Hypothesis H9. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for RBC transfusions on/after Week 5 in the MAHE composite.
- Hypothesis H10. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for prolonged severe (Grade 4) neutropenia (> 5 days) in the MAHE composite.

These 10 hypotheses can be grouped into 3 families:

- Family 1 (F1) includes the hypotheses H1 and H2.
- Family 2 (F2) includes the hypothesis H3, H4, and H5.
- Family 3 (F3) includes the hypotheses H6, H7, H8, H9, and H10.

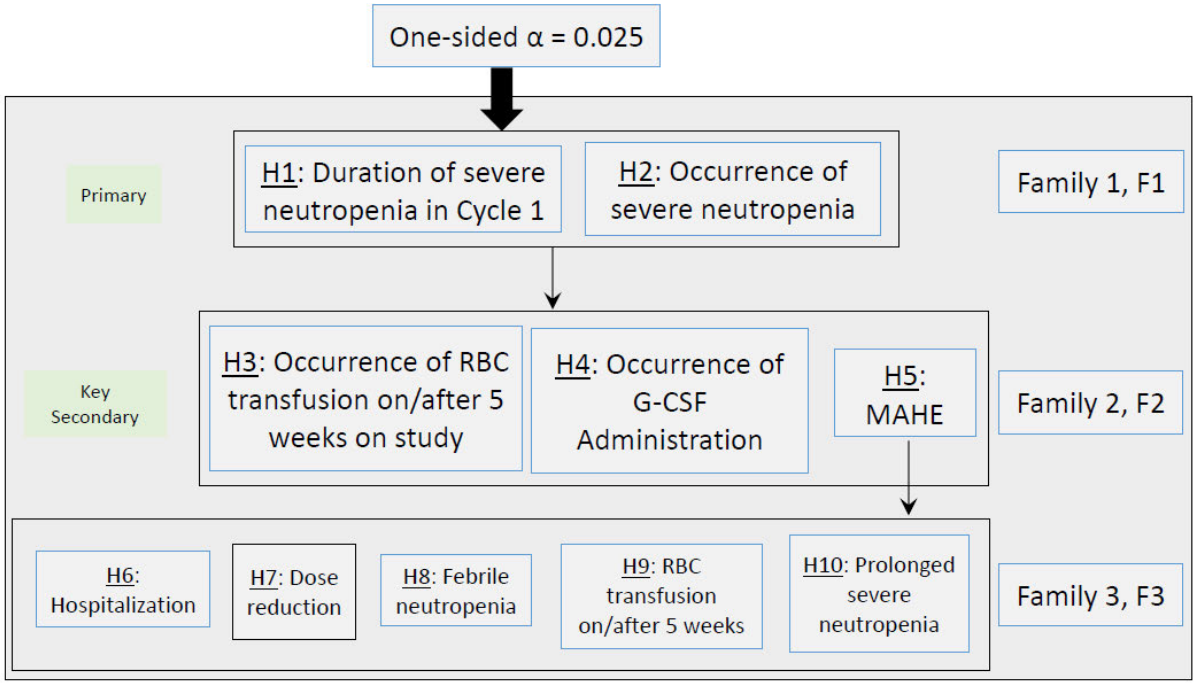
The 1-sided p-values for these 10 comparisons will be used for the multiple testing procedure.

A Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the 10 null hypotheses in the strong sense at a 1-sided α=0.025 level, and it satisfies the positive dependence condition at the 1-sided setting. The procedure is built using the mixture methodology developed in Dmitrienko and Tamhane (2011) and accounts for the logical restrictions among the 10 hypotheses displayed in Figure 13-1 by performing multiplicity adjustments in three steps:

- Step 1. The trilaciclib vs placebo comparisons for Family 1 (hypotheses H1 and H2) are performed using a truncated version of the Hochberg procedure. The truncation parameter γ is set to 0.5.
- Step 2. The trilaciclib vs placebo comparisons for Family 2 (hypotheses H3, H4, and H5) are performed using a truncated version of the Hochberg procedure if there is at least one significance in Step 1. Specifically, the hypotheses H3, H4, and H5 depend on the hypotheses H1 and H2, ie, H3, H4, and H5 are tested only if at least one of the hypotheses H1 and H2 is rejected. The truncation parameter γ is set to 0.5.

- Step 3. The trilaciclib vs placebo comparisons for Family 3 (hypotheses H6, H7, H8, H9, and H10) are performed using the regular Hochberg test if H5 is significant in Step 2.

Figure 13-1 Graphical Display of the Hochberg-based Gatekeeping Procedure for Region 1



The regular Hochberg test is defined in Dmitrienko et al. (2009) and the truncated Hochberg test is defined in Dmitrienko, Tamhane and Wiens (2008). The decision rules used in the regular and truncated Hochberg tests will be detailed in the SAPs. In general terms, the truncated version of the Hochberg test is defined as a convex combination of the regular Hochberg and Bonferroni tests. An important parameter of the truncated Hochberg test is the truncation parameter γ which ranges between 0 and 1. If the truncation parameter γ is set to 0, the truncated Hochberg test simplifies to the Bonferroni test. On the other hand, if the truncation parameter γ is set to 1, the truncated Hochberg test is identical to the regular Hochberg test. The truncated Hochberg test satisfies the separability condition (Dmitrienko, Tamhane and Wiens, 2008) if the truncation parameter γ is strictly less than 1. This condition ensures that in each step of the testing algorithm the error rate can be transferred to the next step provided at least one trilaciclib vs placebo comparison is significant in the current step without inflating the overall type I error rate (Huque, 2016; FDA, 2017).

13.5.3.2. Multiplicity Adjustments in Region 2

The multiplicity problem includes the following 5 hypotheses of no effect:

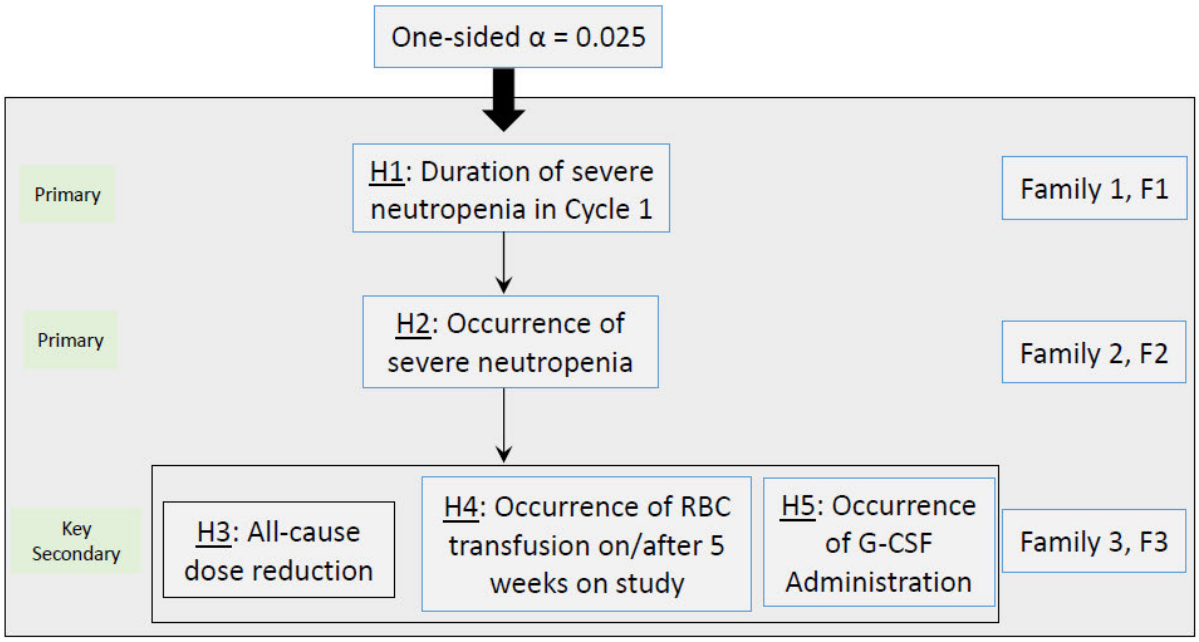
- Hypothesis H1. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H2. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of severe (Grade 4) neutropenia.

- Hypothesis H3. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for the number of all-cause dose reductions.
- Hypothesis H4. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of RBC transfusions on/after Week 5 on study.
- Hypothesis H5. Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of G-CSF administration.

These 5 hypotheses can be grouped into 3 families:

- Family 1 (F1) includes the hypothesis H1.
- Family 2 (F2) includes the hypothesis H2.
- Family 3 (F3) includes the hypotheses H3, H4, and H5.

Figure 13-2 Graphical Display of the Hochberg-based Gatekeeping Procedure for Region 2



Though the testing procedure can be broadly considered as a fixed sequence procedure with the third family consisting of three hypotheses H3, H4, and H5, its implementation can be performed through a similar Hochberg-based gatekeeping procedure as described in Section 13.5.3.1. Hence, the multiplicity adjustments will be performed in three steps as demonstrated in Figure 13-2:

- Step 1. The trilaciclib vs placebo comparisons for Family 1 (hypothesis H1) is performed using a truncated version of the Hochberg procedure. The truncation parameter γ is set to 0.
- Step 2. The trilaciclib vs placebo comparisons for Family 2 (hypothesis H2) is performed using a truncated version of the Hochberg procedure if H1 is significant in Step 1. The truncation parameter γ is set to 0.

- Step 3. The trilaciclib vs placebo comparisons for Family 3 (hypotheses H3, H4, and H5) are performed using the regular Hochberg test if H2 is significant in Step 2.

Based on the proposed testing strategy in Figure 13-2, the study can be potentially claimed to be positive if at least both H1 and H2 are statistically significant.

13.5.4. Analysis of Supportive Secondary Efficacy Endpoints (Antitumor and Myelosuppression)

The detailed derivation for these endpoints along with their analysis methods will be included in the SAPs.

For **Region 1 only**, OS will be considered as a supportive secondary endpoint and will be analyzed according to Section 13.5.2.1.

For **Region 2 only**, the composite MAHE endpoint will be considered a supportive secondary efficacy endpoint to be analyzed as described above (Section 13.5.3).

All the remaining endpoints are relevant to both Regions.

Anti-tumor activity per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the investigator will include the following:

- Objective response (CR or PR)
- Best overall response (BOR)
- Duration of objective response (DOR)
- Progression-free survival (PFS)

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

Duration of Objective Response (DOR) is the time between first objective response of CR or PR and the first date that progressive disease is objectively documented 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 of CR or PR but (i) withdrawal of consent to obtain scans; (ii) lost to follow up; (iii) initiation of subsequent anticancer therapy, or (iv) death, the DOR of this patient will be censored at the earliest date among these four.

PFS is defined as the time (number of months) from date of randomization until date of documented radiologic disease progression per RECIST version 1.1 or death due to any cause, whichever comes first. More specifically, PFS will be determined using all data until the last evaluable visit prior to or on the date of (i) radiographic disease progression per RECIST version 1.1; (ii) withdrawal of consent to obtain scans; or (iii) initiation of

subsequent anticancer therapy, whichever is earlier. Death is always categorized as a confirmed PD event. Censoring methods for patients who do not experience PD or death will be described in the study SAP.

The following endpoints will be used to evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing effects on multiple lineages and current standard of care interventions to treat myelosuppression (neutrophils, RBC, platelets, lymphocytes):

- Occurrence of Grade 3 and 4 hematologic toxicities
- ANC nadir by cycle where ANC nadir is the lowest ANC value that occurred over a chemotherapy cycle.
- Occurrence of RBC transfusions (at any time)
- Occurrence of platelet transfusions
- ANC, hemoglobin, platelet counts, and lymphocyte counts over time
- Occurrence of ESA administration
- Occurrence of systemic antimicrobial administration

[redacted]

13.6. Safety Analyses

Summaries of safety data will be performed using the safety analysis set. Adverse event data will be coded to system organ class and preferred term using MedDRA (Version 17.1 or later). A detailed definition of treatment emergence will be provided in the SAP. The number and percentage of patients experiencing any treatment emergent AEs (TEAE) overall, and by system organ class and preferred term will be tabulated. Adverse events related to treatment will be further summarized by the treatment to which it is attributed (eg, trilaciclib, carboplatin, etoposide, or atezolizumab). Severity will be tabulated based on greatest severity observed for each patient. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be summarized. Infusion-related reactions (IRRs), AEs leading to study drug discontinuation, use of concomitant medications to treat AEs, as well as incidence and severity of AEs of special interest (AESI) for atezolizumab will be tabulated separately.

Observed values and change from baseline in vital signs, ECG intervals, and hematology, clinical chemistry, urinalysis, and liver function parameters will be tabulated at each visit, as

appropriate. Toxicity grades for clinical lab parameters (eg, hematology, chemistry) will be characterized according to CTCAE, Version 4.03, when possible. Shifts in toxicity grades from baseline to each visit, and from baseline to the worst grade during the study will be summarized. Summaries examining maximum and minimum post-baseline changes will consider both scheduled and unscheduled data.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Dose modifications, interruptions, compliance, and patient exposure will be summarized for each study therapy component, where appropriate. This will include, but not limited to the following:

- Occurrence of chemotherapy delays and interruptions
- Occurrence of trilaciclib dose delays and interruptions
- Occurrence of atezolizumab dose delays and interruptions
- Relative dose intensity of carboplatin and etoposide

13.7. Pharmacokinetic Analysis

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

Plasma concentration data will be tabulated descriptively and graphed at each visit and time point. Pharmacokinetic parameters will be calculated with noncompartmental methods (WinNonlin Version 6.3 or higher) based on the plasma concentration-time data. The following PK parameters will be calculated (when data permit their calculation): C_{max}, C_{min}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, CL, and V_z. Pharmacokinetic parameters will be summarized descriptively by visit and analyte. Details will be described in a separate analysis plan.

14. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

15. ETHICS AND PROTECTION OF HUMAN PATIENTS

15.1. Ethical Conduct Statement

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

15.2. Institutional Review Board/Independent Ethics Committee

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

15.3. Informed Consent

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

15.4. Patient Confidentiality

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

15.5. Adherence to the Protocol

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

15.6. Protocol Amendments

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

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

15.7. Patient Compliance

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

15.8. Study Discontinuation

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

16. DATA HANDLING AND RECORD KEEPING

16.1. Data Collection and Retrieval

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

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

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

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

16.2. Data Monitoring Committee

An external DMC will be used to evaluate safety of the study in an ongoing manner (see Section 13.2.2 for further details).

16.3. Investigator Reporting Requirements

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

16.4. Records Retention

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

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

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

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

16.5. Study Monitoring

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

16.6. Audits and Inspections

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

17. PUBLICATION POLICY

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

Initial publication of the results of this study will be of a cooperative nature that may include authors representing the sponsor, investigator(s), and collaborating scientists. Independent publications by involved individuals may follow. Investigators and their institutions agree not to publish or publicly present any interim results of studies without the prior written consent of G1 Therapeutics.

At least 60 days prior to expected submission to the intended publisher or meeting committee, the investigator will submit a copy of the desired presentation (oral or written) or publication manuscript to the sponsor. This review period may be shortened upon mutual consent where circumstances require expeditious review. The sponsor reserves the right to request modification of any publication, presentation or use by the investigator if such activity may jeopardize a patent application, an existing patent, or other proprietary rights. The sponsor shall determine order of authorship of any publication combining all clinical results of this trial.

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19. APPENDICES

APPENDIX 1: Atezolizumab Guidance for the Investigator

APPENDIX 2: Package Insert for Atezolizumab

Tecentriq® (atezolizumab) injection package insert link:
https://www.gene.com/download/pdf/tecentriq_prescribing.pdf

APPENDIX 3: Atezolizumab Adverse Events of Special Interest

APPENDIX 4: Package Inserts for Chemotherapy Agents

Etopophos® (etoposide phosphate) package insert link:
http://packageinserts.bms.com/pi/pi_etopophos.pdf

Etoposide concentrate for solution for infusion 20 mg/mL. Summary of Product Characteristics July 2015 link:
https://www.medicines.org.uk/emc/medicine/30539

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

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

APPENDIX 5: Common Terminology Criteria for Adverse Events (CTCAE) –Version 4.03

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

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

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