Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Etoposide and Carboplatin Chemotherapy

Clinical Study Protocol G1T28-02
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Original Protocol Issue Date: 27 April 2015
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Investigational Phase: 1b/2a

Sponsored by:
G1 Therapeutics
79 T.W. Alexander Drive
4501 Research Commons, Suite 100
Research Triangle Park, NC 27709
919-213-9835

SPONSOR SIGNATURE PAGE

SPONSOR: G1 THERAPEUTICS

I have read and understand the contents of this clinical protocol for Study G1T28-02 dated 15 September 2016 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:

15 Sep 2016

Rajesh Malik, MD Date
Chief Medical Officer, G1 Therapeutics

PROTOCOL SIGNATURE PAGE

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

Principal Investigator:

Principal Investigator Signature	Date
Principal Investigator Name	Institution

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-fluorouracil
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{EDC}	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_{NEDC}	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
CDK2/4/6	cyclin-dependent kinase 2/4/6
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum 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

Abbreviation	Definition
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEG	electroencephalogram
EOI	end of infusion
E/P	etoposide and carboplatin
E/P therapy	etoposide and carboplatin on Day 1 and etoposide on Days 2 and 3 of 21-day cycles
ESA	erythropoietin stimulating agent
FACT	Functional Assessment of Cancer Therapy quality of life instrument
FACT-An	Functional Assessment of Cancer Therapy –Anemia quality of life instrument
FACT-L	Functional Assessment of Cancer Therapy –Lung quality of life instrument
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose
G1	gap 1 phase of the cell cycle
G2	gap 2 phase of the cell cycle
G1T28	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
γH2AX	phosphorylated histone H2AX
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSPC	hematopoietic stem and progenitor cell
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
IRB	institutional review board
IV	intravenous
IWRS	interactive web-response system
LD	longest diameter

Abbreviation	Definition
LDH	lactate dehydrogenase
LS	least square
M	mitosis phase of cell cycle
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
MDR1	p-glycoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	magnetic resonance imaging
MRP1 or 2	multidrug resistance protein 1 or 2
NCI	National Cancer Institute
NCI-H69	human small cell lung cancer cell line
NE	not evaluable
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
PCI	prophylactic cranial irradiation
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PP	per protocol
PR	partial response
PRO	patient-reported outcome
QOL	quality of life
Rb	retinoblastoma protein
RB-1	retinoblastoma gene
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RH	relative humidity
RNA	ribonucleic acid
RNASeq	RNA sequencing
S	synthesis phase of cell cycle in which DNA is replicated
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SCLC	small cell lung cancer
SD	stable disease
SMC	safety monitoring committee
SOP	standard operating procedure
$t_{1/2}$	terminal half-life
T_{max}	time to reach C_{max}
TP53	tumor protein 53
UGT1A1	uridine disphosphate glucuronosyltransferase 1 family, polypeptide A1
ULN	upper limit of normal
Vz	volume of distribution in the terminal elimination phase
WBC	white blood cell
WHO	World Health Organization

3. SYNOPSIS

Title	Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Etoposide and Carboplatin Chemotherapy
Study Rationale	Chemotherapy-induced myelosuppression is a significant issue in cancer treatment, including treatment of SCLC. G1T28 (formerly G1T28-1) is a highly potent and selective cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that causes a transient and reversible gap 1 phase (G1) cell cycle arrest of hematopoietic stem and progenitor cells (HSPCs) within the bone marrow, thus protecting their deoxyribonucleic acid (DNA) from damage by coadministered chemotherapy and preserving long-term function. In animal studies, administration of G1T28 just prior to dose(s) of 5-fluorouracil (5-FU) resulted in a more rapid recovery of all hematopoietic lineages. This effect persisted following administration of multiple cycles of chemotherapy. Bone marrow obtained from mice that received 4 cycles of G1T28 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 G1T28 administered with chemotherapy can preserve stem cell function. The Phase 1a, first-in-human Study G1T28-1-01 demonstrated that G1T28 was well tolerated following administration of a single intravenous (IV) dose. The pharmacokinetics (PK) of G1T28 suggests that drug accumulation following repeated administration is unlikely to occur. Based on PK and pharmacodynamic parameters from the Phase 1a study and a preclinical PK/pharmacodynamic (PK/PD) model, a biologically effective dose (BED) of 192 mg/m^2 of G1T28 was identified. Twenty-four hours following administration of the BED, a significant decrease was noted in the number of bone marrow 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), which persisted at 32 hours. Thus, dosing of G1T28 200 mg/m^2 (rounded up from the BED of 192 mg/m^2) prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles (hereafter referred to as E/P therapy) should maintain the bone marrow HSPCs in G1 arrest during and for several half-lives after chemotherapy administration, thus protecting their DNA from cytotoxic damage. The goals of this study are to assess the safety and tolerability of combining G1T28 with E/P therapy and to evaluate the effect of G1T28 on chemotherapy-induced myelosuppression.
Clinical Phase	1b/2a
Indication	Reduction of chemotherapy-induced myelosuppression

Objectives

	Phase 1b Dose-Finding Portion of Part 1	Phase 2a Expansion Portion of Part 1	Phase 2a Part 2
Primary Objectives			
Assess the DLTs and define the Phase 2 dose of G1T28 administered with E/P therapy	X		
Assess the safety and tolerability of G1T28 administered with E/P therapy	X	X	X
Secondary Objectives			
Assess the PK profile of G1T28	X		
Assess the PK profile of etoposide and carboplatin when administered with G1T28	X		
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of G1T28 administered with E/P therapy	X	X	X
Assess the incidence of febrile neutropenia	X	X	X
Assess the incidence of infections	X	X	X
Assess the utilization of RBC and platelet transfusions	X	X	X
Assess the utilization of hematopoietic growth factors	X	X	X
Assess the utilization of systemic antibiotics	X	X	X
Assess the incidence of chemotherapy dose reductions and dose interruptions overall	X	X	X
Assess the incidence of Grade 2 or greater nephrotoxicity	X	X	X
Assess tumor response based on RECIST, Version 1.1	X	X	X
Assess PFS and overall survival	X	X	X
Exploratory Objectives			
Assess the incidence of mucositis	X	X	X

	Phase 1b Dose-Finding Portion of Part 1	Phase 2a Expansion Portion of Part 1	Phase 2a Part 2
Assess the incidence of alopecia	X	X	X
Assess the incidence of fatigue	X	X	X
Assess patient-reported QOL	X	X	X
Assess immunologic markers			X

DLT = dose-limiting toxicity; E/P therapy = etoposide + carboplatin on Day 1 and etoposide on Days 2 and 3 of 21-day cycles; PFS = progression-free survival; PK = pharmacokinetic; QOL = quality of life; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

Study Design

This is a randomized, double-blind, placebo-controlled, multicenter Phase 1b/2a study of the safety and PK of G1T28 in combination with E/P therapy for patients with newly diagnosed extensive-stage SCLC. The study consists of 2 parts: Part 1 will be a limited Phase 1b, open-label, dose-finding portion followed by a Phase 2a, open-label, expansion portion in up to 18 patients at the selected dose to be used in Part 2. Prior to initiating Part 2, up to a total of 24 patients will be enrolled at the chosen Part 2 dose (6 patients in the Phase 1b dose-finding portion of Part 1 and up to 18 patients in the Phase 2a expansion portion of Part 1). Part 2 will consist of a randomized, double-blind cohort (70 patients will be randomly assigned to G1T28 administered IV with E/P therapy or placebo administered IV with E/P therapy). All parts of the study include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit.

Part 1

The goal of the Phase 1b dose-finding portion of Part 1 is to assess the safety, including dose-limiting toxicities (DLTs), and PK of G1T28 administered at a starting dose of 200 mg/m^2 (derived from Study G1T28-1-01, a Phase 1a, safety, PK, and pharmacodynamic study of G1T28 in healthy male and female patients) on Days 1 to 3 of E/P therapy.

The goal of the Phase 2a expansion cohort of Part 1 is to obtain additional safety and efficacy data for G1T28 in combination with E/P to inform further development in newly diagnosed extensive-stage SCLC.

Six patients will initially be enrolled in the Phase 1b dose-finding portion of Part 1. Depending on the evaluation of DLTs and PK parameters from these initial patients in Cycle 1, additional cohorts of 6 patients may be enrolled at higher or lower doses. The PK profile of G1T28 is well established in healthy subjects, with good estimates of key parameters such as maximum concentration (C_{max}), area under the concentration-time curve (AUC), and Clearance (CL). In addition, the

intersubject variability in these PK parameters is low (see Section 4.2). Therefore, for the initial cohort of 6 patients treated with 200 mg/m^2, the target $AUC_{0\text{-}24.5h}$ is 3100 h•ng/mL. If the mean $AUC_{0\text{-}24.5h}$ is not within 20% of this target (AUC 2480 to 3720 h•ng/mL), the dose of G1T28 will be adjusted in the next cohort of 6 patients to achieve a mean $AUC_{0\text{-}24.5h}$ of 3100 h•ng/mL. Any available PK data from additional cohort(s) of the Phase 1b dose finding portion of Part 1 may be utilized for modifying the G1T28 dose (if required). If the G1T28 dose level for a subsequent cohort requires escalation, the increase will not exceed 30% from the previous dose level. The magnitude of the dose modification is based upon the fact that G1T28 displays linear PK over the dose range studied to date. The adjusted dose, if necessary, will be tested in 6 additional patients enrolled in the Phase 1b dose-finding portion of Part 1, and up to 18 patients will be enrolled at the chosen Part 2 dose in the Phase 2a expansion portion of Part 1, prior to initiating the randomized part (Part 2) of the study.

All dose escalation/de-escalation decisions will be based on Cycle 1 safety data from all patients enrolled into the cohort and available PK data, which will be reviewed by a safety monitoring committee (SMC) comprised of the sponsor, medical monitor, and the principal investigator(s) to determine the next dose level. If the G1T28 dose level for a subsequent cohort is adjusted by the SMC, the SMC may also recommend that all patients currently receiving G1T28 in combination with E/P therapy should have their G1T28 dose adjusted accordingly, starting with their next scheduled cycle. Additional cohorts for the Phase 1b dose-finding portion of Part 1 will be considered based on the review of safety and available PK data by the SMC. The dose for Part 2 will be obtained by utilizing all available safety and available PK data from patients enrolled in the Phase 1b dose-finding portion of Part 1. Once the dose for Part 2 has been established, additional patients will be enrolled at the selected Part 2 dose in a Phase 2a expansion cohort in Part 1 until up to 24 patients in total have been enrolled at that dose. The Phase 2a expansion cohort in Part 1 will complete enrollment before enrollment to Part 2 of the study commences.

Each patient will be evaluated for toxicity during each cycle. The toxicity of G1T28 administered IV with E/P therapy will be assessed by the investigators using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

If there is ≤ 1 dose-limiting toxicity (as defined below) in any of the first cohort of patients (6 patients) during Cycle 1 of the Phase 1b dose-finding portion of Part 1, and the target PK parameters are achieved, then the dose-finding portion of Part 1will end and subsequent patients will be enrolled into the Phase 2a expansion cohort, utilizing a dose of G1T28 200 mg/m^2 in combination with E/P therapy. If an additional cohort(s) of 6 patients is enrolled in the Phase 1b dose-finding portion of Part 1, then the dose for Part 2 will be defined following evaluation of safety and available PK data from the additional cohort(s) of patients and enrollment into the Phase 2a

expansion cohort will commence at that dose.

Dose-limiting toxicities (applicable to Cycle 1 of the Phase 1b dose-finding portion of Part 1) are drug-related toxicities defined as follows:

- Absolute neutrophil count (ANC) < 0.5×10^9/L lasting for ≥ 7 days
- ≥ Grade 3 neutropenic infection/febrile neutropenia
- Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with bleeding
- Unable to start next cycle of chemotherapy due to lack of recovery to an ANC ≥ 1.5×10^9/L and platelet count ≥ 100×10^9/L
- ≥ Grade 3 nonhematologic toxicity (nausea, vomiting, and diarrhea failing maximal medical management; fatigue lasting for > 72 hours)

Toxicities not clearly related to etoposide/carboplatin (E/P) therapy will also be considered for the purposes of determining DLTs.

Part 2

In Part 2, eligible patients will be randomized (1:1 fashion) to G1T28 or placebo administered IV once daily on Days 1 to 3 of E/P therapy. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2). There will be no intrapatient dose modifications of G1T28 in Part 2 of the study.

Criteria for Subsequent Cycles and Study Duration

In both parts of the study, study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator (eg, after completing 6 cycles), whichever occurs first. 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 as scheduled, patients must have an ANC ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and nonhematologic drug-related toxicities (except alopecia) must be ≤ Grade 1 or have returned to baseline. A delay of up to 2 weeks is permitted to allow recovery from any toxicity in order to meet the continuation criteria for organ function. If patients meet the criteria for starting the subsequent cycle as stated in Section 6.1.3, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). If the subsequent 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, as well as on the actual first dosing day of the next cycle. A patient will be discontinued from the study if recovery from any toxicity, in order to meet the continuation criteria for organ function, and any delay for

administrative reasons requires a total delay of > 2 weeks.

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported outcome (PRO) scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study, which is to continue until at least 50% of the patients randomized to Part 2 of the study have died. The G1T28-02 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study.

Safety Assessments

Safety assessments will include monitoring of adverse events (AEs), vital signs measurements, physical examinations, electrocardiograms (ECGs), clinical laboratory studies, infusion-related reactions, tumor response based on RECIST, Version 1.1, progression-free survival (PFS), and overall survival. Safety surveillance reporting of AEs and concomitant medications commences at the time that informed consent is obtained and continues through the Post-Treatment Visit.

An independent data monitoring committee (DMC) will monitor accumulating safety and disposition data approximately every 4 months during the Treatment Phase of Part 2 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.

Tumor Assessment

For tumor assessment, all sites of disease should be assessed radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) at screening and after every even cycle, 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. Assessments should be performed within 7 days of starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (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. Patients with a confirmed PR should also consider PCI after completion of chemotherapy based on the investigator's judgment. 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 positron emission tomography (PET) is used, it should also be accompanied by spiral

	CT or MRI.
Treatment Duration	Study drug administration will continue for each patient until disease progression per RECIST, Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator (eg, after completing 6 cycles), whichever occurs first.
Study Duration	The total study duration is at least 29 months. Part 1 is expected to be approximately 18 months, assuming 12 months of accrual, 2 weeks for screening, 4.5 months of treatment (assuming 6 cycles), and 1 month of safety follow-up. Part 2 will begin after the Part 2 dose is identified from the Phase 1b dose-finding portion of Part 1 and the Phase 2a expansion of Part 1 has completed enrollment, which is expected to occur approximately 12 months after Part 1 begins. Part 2 is expected to be approximately 17 months, assuming 11 months of accrual, 2 weeks of screening, 4.5 months of treatment (assuming 6 cycles), and 1 month of safety follow-up. The Survival Follow-up Phase will continue until at least 50% of the randomized patients in Part 2 have died.
Approximate Number of Patients	Overall, up to 110 patients will be enrolled in the study. In Part 1, approximately 40 patients will be enrolled, assuming up to 3 cohorts. Cohorts will consist of 6 patients each in the Phase 1b dose-finding portion of Part 1 and up to 18 patients in the Phase 2a expansion portion of Part 1 at the selected dose to be used in Part 2. Additional patients may be enrolled in the Phase 1b dose-finding portion of Part 1 if more than 1 cohort is enrolled. In Part 2, 70 patients will be randomly assigned to 1 of 2 groups as follows: G1T28 administered IV with E/P therapy (Group 1) or placebo administered IV with E/P therapy (Group 2).
Number of Study Centers	Up to 80 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 $\geq$ 18 years 2. Unequivocally confirmed diagnosis of SCLC by histology or cytology, preferably including the presence of neuroendocrine features by immunohistochemistry 3. Extensive-stage disease 4. At least 1 target lesion that is unirradiated and measurable by RECIST, Version 1.1 (Eisenhauer 2009) 5. Hemoglobin $\geq$ 9.0 g/dL 6. Absolute neutrophil count $\geq 1.5 \times 10^9$/L 7. Platelet count $\geq 100 \times 10^9$/L 8. Creatinine $\leq$ 1.5 mg/dL OR glomerular filtration rate (GFR) of $\geq$ 60 mL/minute (by Cockcroft-Gault formula [Cockcroft

	and Gault 1976]); creatinine clearance calculated from an isotopic method or 24-hour urine collection may be used instead of an estimated GFR by the Cockcroft-Gault formula 9. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) 10. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases 11. Serum albumin ≥ 3 g/dL 12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 13. Predicted life expectancy of ≥ 3 months 14. Contraception: a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and at baseline. Females must be either postmenopausal, surgically sterile, or using an acceptable method of contraception. Acceptable surgical sterilization techniques are hysterectomy, bilateral tubal ligation with surgery at least 6 months prior to dosing, and bilateral oophorectomy, with surgery at least 2 months prior to dosing. Acceptable methods of contraception are an intrauterine device, contraceptive implant, oral contraceptive (stable dose of the same hormonal contraceptive product for at least 3 months prior to dosing), a vasectomized partner, and a barrier method (condom or diaphragm) during the study and for 3 months after discontinuation of treatment b. For males: Patients with female partner of childbearing potential must agree to use a highly effective form of birth control, which entails the use of oral, injected, or implanted hormonal methods of contraception or an intrauterine device/system by the female partner, in combination with a barrier method (eg, condom, diaphragm, cervical cap) during the study and for 3 months after discontinuation of treatment, and will also refrain from sperm donation for 3 months following completion of the study 15. Able to understand and sign an informed consent
Criteria for Exclusion	A patient will not be eligible for participation in this study if any of the following criteria apply. 1. Prior chemotherapy for limited or extensive-stage SCLC 2. Presence of symptomatic brain metastases requiring

	immediate treatment with radiation therapy or steroids 3. History of other malignancies, except for the following: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated a) in situ carcinoma of the uterine cervix, b) prostate cancer, or c) superficial bladder cancer; or (3) other curatively treated solid tumor with no evidence of disease for ≥ 3 years 4. Uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (Class III or IV as defined by the New York Heart Association [NYHA] functional classification system) 5. Known history of stroke or cerebrovascular accident within 6 months prior to enrollment 6. Serious active infection 7. Psychiatric illness/social situations that would limit study compliance 8. Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol 9. Known human immunodeficiency virus (HIV), known hepatitis B virus (HBV), or known hepatitis C virus (HCV) positive that is symptomatic or requiring active therapy 10. Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response) 11. Receipt of any investigational medication within 4 weeks prior to enrollment 12. Hypersensitivity to any of the components of the formulation of etoposide or etoposide phosphate 13. Hypersensitivity to cisplatin or other platinum-containing compounds, or mannitol 14. Legal incapacity or limited legal capacity 15. Pregnant or lactating women
Chemotherapy Treatment	Carboplatin dose calculated using the Calvert formula with a target 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 each 21-day cycle
Test Articles Dosage and Administration	A starting dose of G1T28 200 mg/m^2 in 250 mL of dextrose 5% in water (D5W) or in sodium chloride solution 0.9% administered as an IV infusion over 30 minutes once daily on Days 1 to 3 of each 21-day cycle prior to the dose(s) of chemotherapy

Comparator Dosage and Administration	Placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% administered as an IV infusion over 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 the following: kinetics of changes in complete blood counts (CBCs); hematologic toxicities, including febrile neutropenia and infections; red blood cell (RBC) and platelet transfusions; hematopoietic growth factor utilization; systemic antibiotic use; chemotherapy dose reductions and dose interruptions; alopecia; mucositis; nephrotoxicity; fatigue; and PROs using the Functional Assessment of Cancer Therapy (FACT) quality of life (QOL) instruments for lung cancer (FACT-L) and anemia (FACT-An).
Safety Evaluation	Safety will be assessed by evaluation of AEs, physical examinations, vital sign measurements, clinical laboratory data, infusion-related reactions, ECGs, tumor response based on RECIST, Version 1.1, PFS, and overall survival.
Pharmacokinetics Evaluation	In the Phase 1b dose-finding portion of Part 1 of the study, blood samples will be collected for the measurement of G1T28, etoposide, and carboplatin concentrations in plasma as described below. <u>Phase 1b dose-finding portion of Part 1: Cycle 1 Day 1</u> Blood samples will be collected at the following time points relative to the start of G1T28 infusion on Cycle 1 Day 1 for all Cohort 1 patients enrolled in the Phase 1b dose-finding portion of Part 1 of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (end of infusion [EOI] of G1T28), 1 (EOI of carboplatin), 1.5, 2 (EOI of etoposide), 2.5, 3, 4.5, 6.5, 8.5 (this time point may be optional if approved by sponsor in advance), and 24.5 (prior to G1T28 dose on Day 2) hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. Collection of PK blood samples from patients enrolled in additional cohorts of the Phase 1b dose-finding portion of Part 1 is optional. <u>Phase 1b dose-finding portion of Part 1: Cycle 1 Day 3</u> Blood samples will be collected at the following time points relative to the start of G1T28 infusion on Cycle 1 Day 3 for all Cohort 1 patients enrolled in the Phase 1b dose-finding portion of Part 1 of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (EOI of G1T28), 1, 1.5 (EOI of etoposide), 2, 2.5, 3.5, 4.5, 6.5, 8.5 (this time point may be optional if approved by sponsor in advance), and 24.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. Collection of PK blood samples from patients enrolled in additional cohorts of the Phase 1b dose-finding portion of Part 1 is optional. Pharmacokinetic parameters (eg, C_{max}, 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 G1T28, etoposide, and carboplatin plasma concentration-time data.

	Pharmacokinetic samples may also be obtained from additional patients in the Phase 2a expansion cohort of Part 1 and Part 2 depending on the outcome of initial Phase 1b PK analysis.
Patient-Reported Outcomes	Functional Assessment of Cancer Therapy QOL instruments for lung cancer (FACT-L) and anemia (FACT-An)
Immunologic Marker Assessment	In Part 2 of the study, peripheral blood samples will be collected at predose on Day 1 of Cycles 1, 3, and 5; at the Post-Treatment Visit; and at 60 days after the Post-Treatment Visit.
Statistical Analysis	Data will be summarized separately by study part (Part 1 and Part 2). Data from Part 1 will be summarized descriptively by dose level, if applicable, and overall. Data from Part 2 will be summarized descriptively by treatment group and overall. Treatment differences between treatment groups for Part 2 will be calculated as G1T28 + E/P therapy minus Placebo + E/P therapy. Select safety summaries will include combined data from both Parts 1 and 2 of the study. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, and minimum and maximum values. The descriptive summaries of time to event data will include median, twenty-fifth and seventy-fifth percentiles, and standard error. All data will be listed for all patients. This study is descriptive in nature, and no formal hypothesis testing will be performed across treatment groups. All confidence intervals (CIs) will be 95%, unless stated otherwise. A DMC will review accumulating safety and disposition data during the Treatment Phase for patients randomized in Part 2. The final analysis will be performed after all patients have completed the Post-Treatment Visit. A supplemental analysis including the cumulative data collected during the Survival Follow-up Phase will be completed at the end of study. The full analysis set (FAS) includes all patients who received at least 1 dose of study drug and will be the primary population for efficacy and exploratory endpoints. Full analysis set analyses will be conducted on the basis of the assigned treatment. The safety population includes all patients who received at least 1 dose of study drug and will be the population used for the analysis of safety endpoints. The safety population will be conducted on the basis of the actual treatment received. A per-protocol (PP) subset may also be used to analyze select endpoints and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The PK analysis set will include all dosed patients in the Phase 1b dose-finding portion of Part 1 with evaluable PK data. Summaries of efficacy will be performed using the FAS on hematologic kinetics, hematologic toxicity, infections, growth factor and antibiotic use, transfusions, chemotherapy exposure, and patient-reported QOL scores. Select summaries will also be repeated in the PP analysis set. Unless noted otherwise, hematologic endpoints will be summarized separately by each parameter type (ie, ANC,

	lymphocytes, etc.). Analyses comparing treatment groups for Part 2 will adjust for baseline ECOG and other relevant parameters. Event rates will be calculated based on cumulative E/P exposure to account for potential differences in E/P exposure across treatment arms. Summaries of safety data will be performed using the safety population. 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. The incidence rates adjusted by cumulative exposure will also be presented overall and by cycle. Absolute values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters will be tabulated at each visit during the Treatment Phase. Toxicities for clinical labs will be characterized according to the CTCAE, Version 4.03. Shifts in toxicity grades from baseline to each visit will be summarized. Overall disease responses as determined by RECIST, Version 1.1 will be summarized by response level at each visit and best overall response. Progression-free survival and overall survival will be summarized using Kaplan-Meier methods. Blood samples will be collected in the Phase 1b dose-finding portion of Part 1 of the study for the determination of G1T28, etoposide, and carboplatin plasma concentrations. Plasma PK parameters will be calculated for each analyte, when possible, including C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, V_z, and CL. 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 graphed for each blood sampling day. Pharmacokinetic parameters will be calculated using noncompartmental methods based on the plasma concentration-time data. Pharmacokinetic parameters will be summarized descriptively by visit and analyte. If applicable, G1T28 PK data will also be summarized by dose level.
Rationale for Number of Patients	The sample size for this study is determined by clinical rather than statistical considerations. Up to 40 patients (open-label, dose-finding cohort[s] and an open-label, expansion cohort) will be enrolled in Part 1 of the study and 70 patients will be enrolled in Part 2 of the study (randomized).

4. INTRODUCTION

4.1. Background

Chemotherapy-induced myelosuppression continues to represent the major dose-limiting toxicity (DLT) of cytotoxic chemotherapy, including the etoposide and platinum (cisplatin or carboplatin) combination used to treat extensive-stage small cell lung cancer (SCLC) (Schmittel 2006; Socinski 2009). Whether using cisplatin or carboplatin, the combination of a platinum agent with etoposide results in significant myelosuppression (neutropenia 47% to 92%, leukopenia 8% to 66%, thrombocytopenia 10% to 46%, and anemia 7% to 34%) (Eckardt 2006; Noda 2002; Hanna 2006; Socinski 2009; Hermes 2008; Schmittel 2011). Myelosuppression is the source of many of the important side effects of cancer treatment, such as infection, sepsis, bleeding, and fatigue, leading to the need for hospitalizations, hematopoietic growth factor support, and transfusions (red blood cells [RBCs] and/or platelets). Moreover, clinical concerns raised by myelosuppression commonly lead to chemotherapy dose reductions and limit therapeutic dose intensity.

G1T28 (formerly G1T28-1) is a highly potent and selective, reversible, cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that transiently induces gap 1 (G1) phase (resting phase in the cell cycle in which cells exist in a quiescent state) cell cycle arrest of hematopoietic stem and progenitor cells (HSPCs) in the bone marrow. These cells are dependent upon CDK4/6 for proliferation and enter the G1 phase of the cell cycle upon exposure to G1T28. When the HSPCs are transiently arrested in the G1 phase of the cell cycle, they are more resistant to the deoxyribonucleic acid (DNA) damaging effects of chemotherapy, thus potentially reducing subsequent myelosuppression. The initial indication for intravenous (IV) G1T28 is the reduction of chemotherapy-induced myelosuppression.

The principal component of this therapeutic approach is to transiently arrest HSPCs in the G1 phase of the cell cycle while chemotherapy is administered. It is imperative that this therapeutic approach provides selective bone marrow protection without antagonizing the tumor efficacy of chemotherapy. To ensure this second feature, patients are required to have CDK4/6-indpendent tumors. The downstream target of CDK4/6 is the retinoblastoma (Rb) protein, which is phosphorylated upon CDK4/6 activation, allowing the cell to enter into the S phase of the cell cycle (synthesis phase of cell cycle in which DNA is replicated). In order to promote G1 cell cycle arrest by utilizing a CDK4/6 inhibitor, a functional Rb protein is required. For SCLC, historical reports have consistently shown the most prevalent inactivated tumor suppressor genes are tumor protein 53 (TP53) and retinoblastoma 1 (RB-1) (D'Amico 1992; Heighway 2004; Yuan 1999; Cagle 1997; Gouyer 1994), and it has been accepted that almost all cases of SCLC are functionally Rb null. In addition, 2 recent reports provided a detailed characterization of the genomic landscape of SCLC using next generation sequencing approaches, including full exome sequencing, transcriptome profiling by RNA sequencing (RNASeq), copy number analyses, and limited whole genome sequencing to identify translocations (Peifer 2012; Rudin 2012). These reports confirmed what had been previously proposed in studies that examined a smaller number of tumors, namely that concomitant inactivation of TP53 and RB-1 are driver mutations and occur nearly universally in SCLC. Consistent with these data, preclinical in vitro and in vivo studies have demonstrated that G1T28 exposure prior to chemotherapy does not diminish the effect of

chemotherapy in tumors that are RB-1 inactive, including SCLC. Therefore, as a result of near universal RB-1 inactivation, SCLC is inherently CDK4/6-independent, which should allow selective protection of the HSPCs but not the tumor from the effects of chemotherapy.

4.2. Summary of Clinical Data

A brief summary of the clinical data is provided in the following sections. Detailed information is presented in the G1T28 Investigator's Brochure (IB).

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

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

Following a single 30-minute IV infusion of G1T28, 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 G1T28 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 G1T28. The elimination kinetics of G1T28 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 G1T28 suggests that drug accumulation following repeated administration is unlikely to occur. Urinary excretion appears to be a minor route of elimination for unchanged G1T28.

G1T28 showed positive pharmacodynamic effects in 2 assays. Dose-dependent inhibition of ex vivo whole blood stimulation occurred following a single IV infusion of G1T28 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 G1T28 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.

4.3. Summary of Nonclinical Data

A brief summary of the nonclinical data is provided in the following sections. Detailed information is presented in the G1T28 IB.

4.3.1. Pharmacology Studies

Through a structure-based design approach to optimize potency, selectivity, and drug metabolism and PK properties, G1 Therapeutics, Inc. identified G1T28 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 G1T28-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 G1T28 with myelosuppressive chemotherapy leads to improved CBC recovery of all blood lineages and increased survival. In addition, administration of G1T28 with every cycle of the highly myelosuppressive chemotherapy 5-fluorouracil (5-FU) for a total of 4 cycles demonstrated that the reduction in chemotherapy-induced myelosuppression persisted following Cycle 4. While the extent and duration of nadir in CBCs worsened after each cycle of 5-FU administered alone, coadministration of G1T28 with 5-FU ameliorated this worsening effect and the animals that received G1T28 + 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, G1T28 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 G1T28 + 5-FU compared with 5-FU alone. In addition, bone marrow obtained from mice that received 4 cycles of G1T28 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 G1T28 administered with chemotherapy can preserve stem cell function.

Retinoblastoma 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 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 G1T28. To expand these findings in vivo, G1T28 was tested alone and in combination with topotecan or an etoposide and carboplatin (E/P) combination regimen in a cell-based xenograft SCLC model (H69) in immune-deficient mice. G1T28 administered alone or 30 minutes before E/P or topotecan was well tolerated, with no additive weight loss or toxicity. Single agent G1T28 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 G1T28 and topotecan was superior to topotecan alone during dosing and the addition of G1T28 extended the statistically significant ($p < 0.05$) antitumor effect of topotecan after dosing. Thus, G1T28 was well tolerated and did not antagonize the effects of chemotherapy in a CDK4/6-independent (RB-1 inactive) SCLC tumor model.

4.3.2. Pharmacokinetic Studies

Pharmacokinetic studies in rats and dogs showed that the relationship between dose level and plasma exposure to G1T28 was generally similar between males and females and did not change with repeated daily dosing. Exposure to G1T28 increased with dose level, but not always proportionally. Plasma half-life values for G1T28 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 G1T28 below 100 µM (44,600 ng/ml). Drug interactions based on G1T28 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 G1T28-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 G1T28-02, IV G1T28 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 study, PK of etoposide, carboplatin, and G1T28 will be assessed on Days 1 and 3 of the first cycle. In addition, frequent CBCs will be assessed. Since myelotoxicity is the major toxicity of etoposide, this will be monitored closely in this study.

In vitro inhibition studies with membrane transporter model systems also suggest G1T28 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. G1T28 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 G1T28 inhibition of OCT2, MATE1, or MATE2-K is not expected.

4.3.3. Toxicity and Safety Studies

The toxicity of IV and oral G1T28 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 G1T28 clinical drug product with human blood was evaluated in vitro.

For further information, please refer to the G1T28 IB.

4.3.4. Potential Risks

When administered IV daily for 7 days, G1T28 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 G1T28 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 G1T28 suggest that potential side effects in human patients might include the following:

- Pulmonary macrophage accumulation: In rats, daily oral doses of G1T28 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 G1T28 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 G1T28.

- Increased heart rate: In dogs, single IV doses of G1T28 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 G1T28 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 G1T28 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.

Although G1T28 induced micronucleus formation in human lymphocytes exposed in vitro, G1T28 is not considered to pose a hazard to human patients, as G1T28 was negative for mutagenic potential in a Good Laboratory Practice (GLP) (and non-GLP) Ames assay, and did not induce phosphorylated histone H2AX (γH2AX) formation in primary human fibroblasts. In the present study, G1T28 will be administered in conjunction with etoposide/carboplatin, which presents a genotoxic hazard to human subjects. In this context, any slight additional genotoxic hazard posed by G1T28 is negligible.

In female rats, daily administration of G1T28 for 7 days resulted in lower ovary and uterus weights and more rats in metestrus/diestrus, and these effects were reversible within 2 weeks after the last dose. These findings in rats raise the possibility that G1T28 may affect menstrual cycling in women; however, no studies have been done specifically to evaluate the effects of G1T28 on fertility in animals of either sex. For men, studies in rats and dogs do not suggest any potential for impairment of fertility; specifically, there were no pathologic findings in reproductive organs of male rats or dogs given daily doses of G1T28 for 7 days. Nevertheless, patients who are pregnant or lactating should not receive G1T28. Heterosexual couples in which the female is of childbearing potential must use appropriate birth control methods.

The nonclinical package as a whole indicates that rats and dogs were appropriate species for evaluating the toxicity of G1T28. In both species, the toxicity profile was similar.

4.4. Study and Dose Rationale

Chemotherapy-induced myelosuppression is a significant issue in cancer treatment, including treatment of SCLC. G1T28 is a highly potent and selective CDK4/6 inhibitor that induces a transient and reversible G1 cell cycle arrest of HSPCs within the bone marrow, thus protecting their DNA from damage by coadministered chemotherapy and preserving long-term function. In animal studies, administration of G1T28 just prior to dose(s) of 5-FU resulted in a more rapid recovery of all hematopoietic lineages. This effect persisted following administration of multiple cycles of chemotherapy. Bone marrow obtained from mice that received 4 cycles of G1T28 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 G1T28 administered with chemotherapy can preserve stem cell function.

Since inactivation of 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-null cells are resistant to CDK4/6 inhibition. In vivo, G1T28 administered alone or 30 minutes before E/P or topotecan was well tolerated and did not antagonize the effects of chemotherapy in a cell-based xenograft model (H69) representing SCLC in immune-deficient mice (see details in Section 4.3.1).

Study G1T28-1-01 was a Phase 1a, safety, PK, and pharmacodynamic study of G1T28. Forty-five healthy male and female subjects were enrolled into 7 dose cohorts where G1T28 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). G1T28 was well tolerated, with no DLTs or SAEs reported. Additionally, over the dose range of 6 to 192 mg/m^2, C_{max} increased in a dose-proportional manner, total systemic (AUC) exposure increased more than dose proportionally, and clearance (CL) was relatively constant. The PK of G1T28 suggests that drug accumulation following repeated administration is unlikely to occur. Based on PK/PD parameters from the Phase 1a study and a preclinical PK/PD model, a BED of 192 mg/m^2 of G1T28 was identified. Twenty-four hours following administration of the BED, a significant decrease was noted 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 G1T28 200 mg/m^2 (rounded up from the BED of 192 mg/m^2) prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles (hereafter referred to as E/P therapy) should maintain the bone marrow HSPCs in G1 arrest during and for several half-lives after chemotherapy administration, thus protecting their DNA from cytotoxic damage. The goals of this study are to assess the safety and tolerability of combining G1T28 with E/P therapy and to evaluate the effect of G1T28 on chemotherapy-induced myelosuppression.

4.5. Risk/Benefit Assessment

G1T28 is being developed to reduce chemotherapy-induced myelosuppression, which is a significant issue. 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 4.4, the BED of IV G1T28 is 192 mg/m^2 and a dose of 200 mg/m^2 will be used as the starting dose for administration on Days 1 to 3 of every 21-day cycle of E/P therapy in the present study. In conclusion, the potential benefits of combining G1T28 at a dose of 200 mg/m^2 with E/P therapy to protect the bone marrow HSPCs outweigh the potential risks.

5. STUDY OBJECTIVES

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

Table 5-1 G1T28-02: Study Objectives

	Phase 1b Dose-Finding Portion of Part 1	Phase 2a Expansion Portion of Part 1	Phase 2a Part 2
Primary Objectives			
Assess the DLTs and define the Phase 2 dose of G1T28 administered with E/P therapy	X		
Assess the safety and tolerability of G1T28 administered with E/P therapy	X	X	X
Secondary Objectives			
Assess the PK profile of G1T28	X		
Assess the PK profile of etoposide and carboplatin when administered with G1T28	X		
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of G1T28 administered with E/P therapy	X	X	X
Assess the incidence of febrile neutropenia	X	X	X
Assess the incidence of infections	X	X	X
Assess the utilization of RBC and platelet transfusions	X	X	X
Assess the utilization of hematopoietic growth factors	X	X	X
Assess the utilization of systemic antibiotics	X	X	X
Assess the incidence of chemotherapy dose reductions and dose interruptions overall	X	X	X
Assess the incidence of Grade 2 or greater nephrotoxicity	X	X	X
Assess tumor response based on RECIST, Version 1.1	X	X	X
Assess PFS and overall survival	X	X	X
Exploratory Objectives			
Assess the incidence of mucositis	X	X	X
Assess the incidence of alopecia	X	X	X
Assess the incidence of fatigue	X	X	X
Assess patient-reported QOL	X	X	X
Assess immunologic markers			X

DLT = dose-limiting toxicity; E/P therapy = etoposide + carboplatin on Day 1 and etoposide on Days 2 and 3 of 21-day cycles; PFS = progression-free survival; PK = pharmacokinetic; QOL = quality of life; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

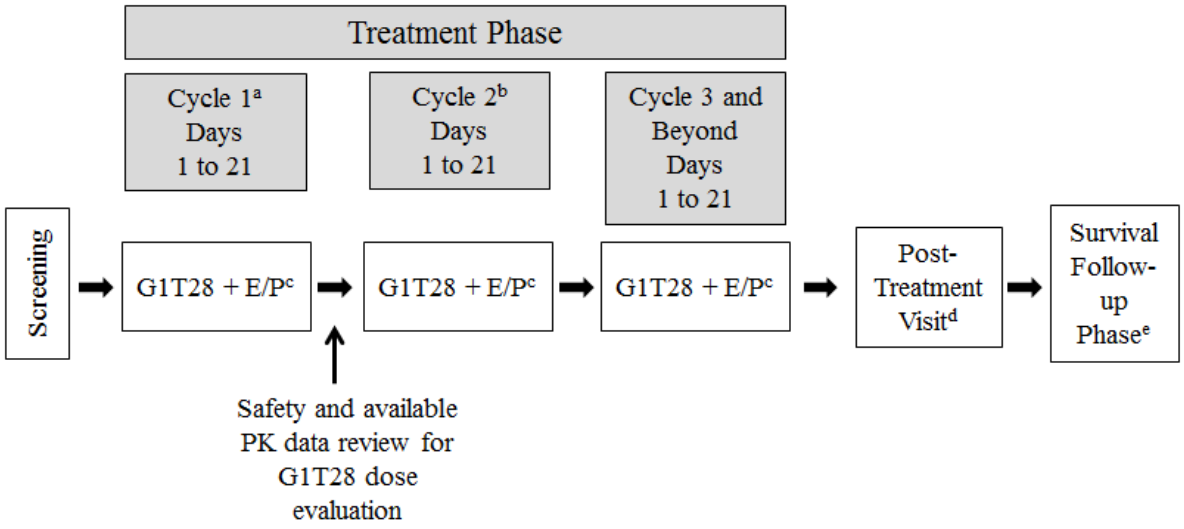
This is a randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2a study of the safety and PK of G1T28 in combination with E/P therapy for patients with newly diagnosed extensive-stage SCLC. The study consists of 2 parts: Part 1 will be a limited Phase 1b, open-label, dose-finding portion followed by a Phase 2a, open-label, expansion portion in up to 18 patients at the selected dose to be used in Part 2. Prior to initiating Part 2, up to a total of 24 patients will be enrolled at the chosen Part 2 dose (6 patients in the dose-finding portion of Part 1 and up to 18 patients in the Phase 2a, open-label, expansion portion of Part 1). Part 2 will consist of a randomized, double-blind cohort (70 patients will be randomly assigned to G1T28 administered IV with E/P therapy or placebo administered IV with E/P therapy). All parts of the study include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit.

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 sending to a central pathology laboratory to confirm the diagnosis of SCLC. If central pathology review does not confirm SCLC diagnosis, the patient may be withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor. Available tissue after confirming the diagnosis of SCLC will be banked for assessment of relevant DNA, ribonucleic acid (RNA), and protein markers, such as those involved in the CDK4/6 pathway.

6.1.1. Part 1

The goal of the Phase 1b dose-finding portion of Part 1 is to assess the safety, including DLTs (see Section 6.1.1.1), and PK (see Section 6.1.1.2) of G1T28 administered at a starting dose of 200 mg/m^2 (derived from Study G1T28-1-01, a Phase 1a, safety, PK, and pharmacodynamic study of G1T28 in healthy male and female patients) once daily on Days 1 to 3 of E/P therapy (Figure 6-1).

Figure 6-1 Study Schema: Phase 1b Dose-Finding Portion of Part 1



E/P = etoposide + carboplatin

a Safety and available PK data from Cycle 1 will be considered in making dose escalation/de-escalation decisions (if required) and enrolling additional cohorts

b G1T28 + E/P will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). The tumor should be assessed after every even cycle using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Assessments should be performed within 7 days of starting the subsequent cycle.

c G1T28 will be administered prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles

d Patients will return to the study center for a Post-Treatment Visit at 30 + 3 days after the last dose of study drug.

e The Survival Follow-up Phase will continue until at least 50% of the patients randomized to Part 2 of the study have died.

6.1.1.1. Definition of Dose-Limiting Toxicities (Applicable to Cycle 1 of the Phase 1b Dose-Finding Portion of Part 1)

Dose-limiting toxicities are drug-related toxicities defined as follows:

- Absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L lasting for $\geq$ 7 days
- $\geq$ Grade 3 neutropenic infection/febrile neutropenia
- Grade 4 thrombocytopenia or $\geq$ Grade 3 thrombocytopenia with bleeding
- Unable to start next cycle of chemotherapy due to lack of recovery to an ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L
- $\geq$ Grade 3 nonhematologic toxicity (nausea, vomiting, and diarrhea failing maximal medical management; fatigue lasting for > 72 hours)

Toxicities not clearly related to etoposide/carboplatin (E/P) therapy will also be considered for the purposes of determining DLTs.

6.1.1.2. Criteria for Adjusting G1T28 Dose Based on Pharmacokinetic Parameters

The PK profile of G1T28 is well established in healthy subjects, with good estimates of key parameters such as C_{max}, AUC, and CL. In addition, the intersubject variability in these PK parameters is low (see Section 4.2). However, patients with SCLC enrolled in this study will likely be older and have more comorbidities compared with subjects enrolled in the Phase 1a G1T28-1-01 study, and therefore, could demonstrate differences in PK.

Based on the observed PK profile of G1T28 in Study G1T28-1-01, the extrapolated $AUC_{0\text{-}24.5h}$ for a 200 mg/m^2 dose is 3100 h•ng/mL. If the mean $AUC_{0\text{-}24.5h}$ in the initial cohort of patients (6 patients) in the Phase 1b, dose-finding portion of Part 1 is not within 20% of the target (eg, 2480 to 3720 h•ng/mL), then the dose of G1T28 will be adjusted in the next cohort of 6 patients to achieve a mean $AUC_{0\text{-}24.5h}$ of 3100 h•ng/mL. The magnitude of the dose modification is based upon the fact that G1T28 displays linear PK over the dose range studied to date. Any available PK data from additional cohort(s) of the Phase 1b dose-finding portion of Part 1 may be utilized for modifying the G1T28 dose (if required). If the G1T28 dose level for a subsequent cohort requires escalation, the increase will not exceed 30% from the previous dose level. A G1 cell cycle arrest of a minimum of 24 hours after G1T28 administration is desired to ensure that the bone marrow arrest is maintained long enough to avoid releasing HSPCs into the S (DNA synthesis) phase of the cell cycle in the presence of high concentrations of chemotherapy and thereby potentially exacerbating myelosuppression.

If the dose is adjusted due to DLTs and the PK was within the expected target range, then a new target $AUC_{0\text{-}24.5h}$ will be calculated for the modified dose as follows:

$Y = 2.11 + 1.1*X$, where Y is the $\ln(AUC_{0\text{-}24.5})$ h*ng/mL and X is the ln(dose) mg/m^2

6.1.1.3. G1T28 Dose Evaluation

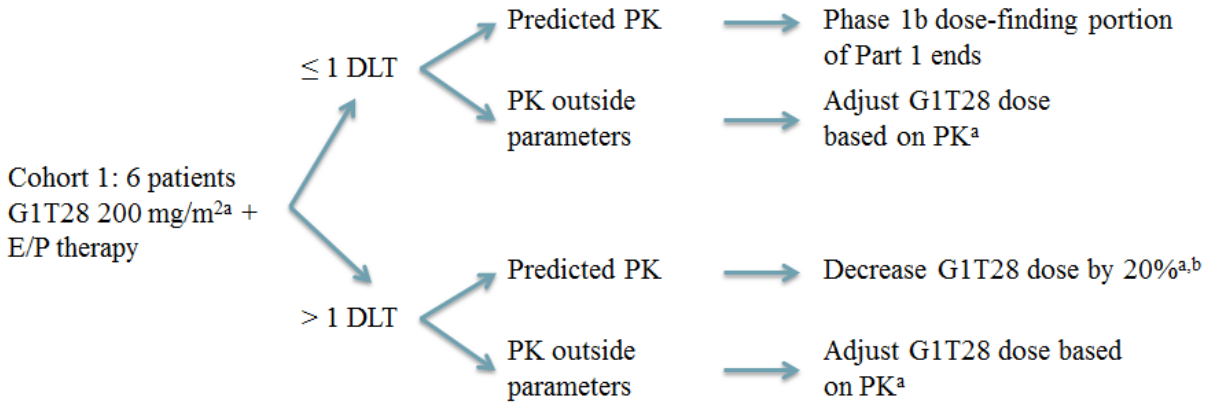
Six patients will initially be enrolled into the Phase 1b, dose-finding portion of Part 1 and will receive G1T28 200 mg/m^2 in combination with standard E/P therapy (see Section 8.1). Safety and available PK parameters from this initial cohort of 6 patients during Cycle 1 will be considered in making dose escalation/de-escalation decisions (if required). If a patient is withdrawn prior to completing all assessments in Cycle 1 for reasons other than toxicity in any cohort in the Phase 1b, dose-finding portion of Part 1, the patient will be replaced. G1T28 dose evaluation criteria are listed below and are presented as a decision tree in Figure 6-2. While the dose evaluation criteria below will be used to guide all dose decisions, the SMC will be responsible for all dose and cohort recommendations.

- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of the Phase 1b, dose-finding portion of Part 1 and the available G1T28 PK parameters are as predicted (Section 6.1.1.2), the dose-finding portion of Part 1 will end and subsequent patients will be enrolled into the Phase 2a expansion cohort of Part 1, utilizing a dose of G1T28 of 200 mg/m^2 in combination with E/P therapy.
- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of the Phase 1b dose-finding portion of Part 1, and the available G1T28 PK parameters suggest that the G1T28 dose needs to be escalated or de-escalated (see Section 6.1.1.2), a second cohort

of 6 patients will be enrolled at the higher or lower predicted G1T28 dose in combination with E/P therapy. For assessment of data from the second cohort enrolled in the Phase 1b dose-finding portion of Part 1, please see the decision tree in Figure 6-2.

- If there is > 1 DLT in the first cohort of 6 patients during Cycle 1 of the Phase 1b dose-finding portion of Part 1 and the available G1T28 PK parameters suggest that the G1T28 dose needs to be escalated or de-escalated (ie, in order to increase or decrease the magnitude and duration of G1 cell cycle arrest of HSPCs predicted by the PK/PD model and data from the Phase 1a Study G1T28-1-01; see Section 6.1.1.2), a second cohort of 6 patients will be enrolled at the modified G1T28 dose in combination with E/P therapy. For assessment of data from the second cohort enrolled in the Phase 1b dose-finding portion of Part 1, please see the decision tree in Figure 6-2.
- If there is > 1 DLT in the first cohort of 6 patients enrolled in the Phase 1b dose-finding portion of Part 1 and the available G1T28 PK parameters from these 6 patients are as predicted (Section 6.1.1.2), the dose of G1T28 should be decreased to 160 mg/m^2 and an additional 6 patients should be enrolled at the modified G1T28 dose in combination with E/P therapy. For assessment of data from the second cohort enrolled in the Phase 1b dose-finding portion of Part 1, please see the decision tree in Figure 6-2.
- If there is > 1 DLT following a G1T28 dose of 160 mg/m^2 in combination with E/P therapy in the second cohort of patients and if available, PK parameters are as predicted (Section 6.1.1.2), an additional cohort of 6 patients will be enrolled at a further decreased G1T28 dose of 130 mg/m^2 in combination with E/P therapy. For assessment of data from the third cohort enrolled in the Phase 1b dose-finding portion of Part 1, please see the decision tree in Figure 6-2.
- If there is > 1 DLT following the second dose reduction of G1T28 and if available, PK parameters from the third cohort are as predicted (Section 6.1.1.2), no further dose modifications will be made and the study will be terminated.
- At any time, if ≥ 2 DLTs are observed in any given cohort, further enrollment into that cohort will be stopped until the SMC can review the available data and make dose and cohort recommendations.

Figure 6-2 G1T28 Dose Evaluation in the Phase 1b Dose-Finding Portion of Part 1



a Assess the adjusted G1T28 dose in the next cohort of 6 patients based on DLTs and PK (if available) per the decision tree

b Maximum of 2 G1T28 dose reductions are allowed

All dose-escalation/de-escalation decisions will be based on Cycle 1 safety data from all patients enrolled into the cohort and available PK data and will be reviewed by a safety monitoring committee (SMC) comprised of the sponsor, medical monitor, and the principal investigator(s) to determine the next dose level. If the G1T28 dose level for a subsequent cohort is adjusted by the SMC, the SMC may also recommend that all patients currently receiving G1T28 in combination with E/P therapy should have their G1T28 dose adjusted accordingly, starting with their next scheduled cycle. Additional cohorts for the Phase 1b dose-finding portion of Part 1 will be considered based on review of the safety data from all patients enrolled into the cohort and available PK data by the SMC. The dose for Part 2 will be obtained by utilizing all available safety and available PK data from patients enrolled in Part 1. Once the dose for Part 2 has been established, additional patients will be enrolled at the selected Part 2 dose in a Phase 2a expansion cohort in Part 1 until up to a total of 24 patients (6 from the Phase 1b dose-finding portion of Part 1 and up to 18 from the Phase 2a expansion cohort) have been enrolled at that dose. The Phase 2a expansion cohort in Part 1 will complete enrollment before enrollment into Part 2 commences.

There will be no intrapatient dose modifications of G1T28 in the Phase 2a expansion cohort of Part 1 and Part 2 of the study.

Each patient will be evaluated for toxicity during each cycle. The toxicity of IV G1T28 administered with E/P therapy will be assessed by the investigators using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

6.1.1.4. Safety Monitoring Committee

The SMC will be set up to review safety of G1T28 for all patients enrolled in the Phase 1b dose-finding portion of Part 1 of the study. The SMC will consist of the clinical investigator(s), the medical monitor, and G1 Therapeutics representatives and/or designees. During the Phase 1b dose-finding portion of Part 1, the SMC will review any DLTs, SAEs, PK, and all other available data. The committee will make recommendations for dose escalation/de-escalation based on the criteria listed in Sections 6.1.1.1 to 6.1.1.3. While the dose evaluation criteria will be used to guide all dose decisions, the SMC will be responsible for all dose and cohort recommendations, including any adjustments to the PK collection schedule. If the G1T28 dose level for a subsequent cohort is adjusted by the SMC, the SMC may also recommend that all patients currently receiving G1T28 in combination with E/P therapy should have their G1T28 dose adjusted accordingly, starting with their next scheduled cycle.

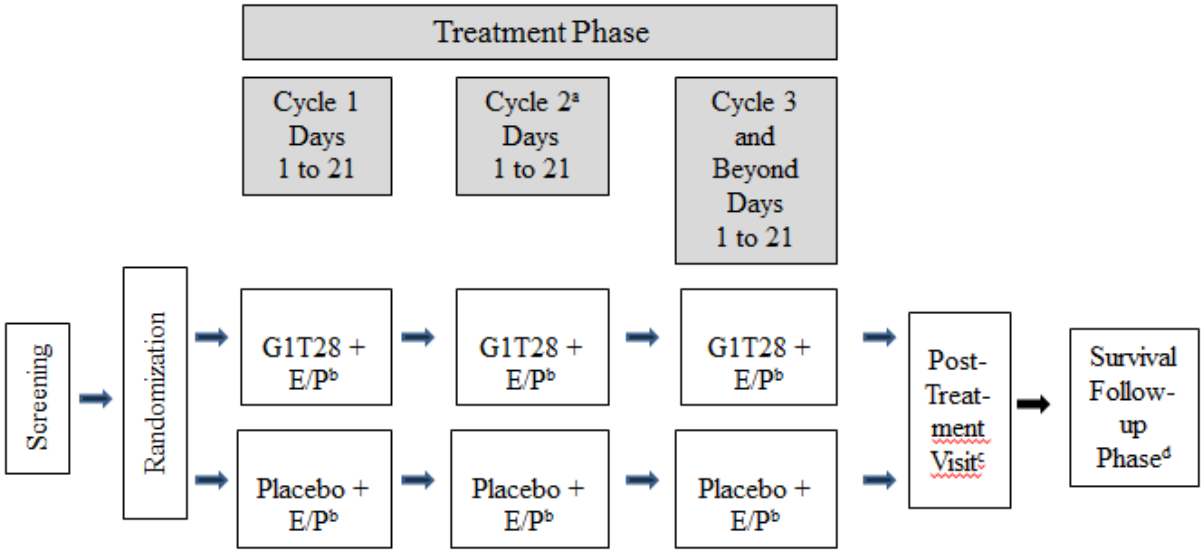
In the Phase 2a expansion cohort of Part 1, the SMC will review any SAEs, efficacy, and all other available data. The SMC may make recommendations for continuing with the Phase 2a expansion cohort in Part 1 with enrollment of up to 18 patients, or moving to Part 2 based on safety and efficacy.

6.1.2. **Part 2**

In Part 2, eligible patients will be randomized (1:1 fashion) to G1T28 or placebo administered IV once daily on Days 1 to 3 of E/P therapy (Figure 6-3). Randomization will

be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2). There will be no intrapatient dose modifications of G1T28 in Part 2 of the study.

Figure 6-3 Study Schema: Part 2



E/P = etoposide + carboplatin

a G1T28 + E/P will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). The tumor should be assessed after every even cycle using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Assessments should be performed within 7 days of starting the subsequent cycle.

b G1T28 will be administered prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles

c Patients will return to the study center for a Post-Treatment Visit at 30 + 3 days after the last dose of study drug.

d The Survival Follow-up Phase will continue until at least 50% of the patients randomized to Part 2 of the study have died.

An independent data monitoring committee (DMC) will monitor accumulating safety and disposition data approximately every 4 months during the Treatment Phase of Part 2 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.

6.1.3. Criteria for Subsequent Cycles and Study Duration

In all parts of the study, study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator (eg, after completing 6 cycles), whichever occurs first. 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 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 ≤ Grade 1 or have returned to baseline

A delay of up to 2 weeks is permitted to allow recovery from any toxicity in order to meet the continuation criteria for organ function. If patients meet the criteria for starting the subsequent cycle as described above, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). If the subsequent 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, as well as on the actual first dosing day of the next cycle. A patient will be discontinued from the study if recovery from any toxicity, in order to meet the continuation criteria for organ function, and any delay for administrative reasons requires a total delay of > 2 weeks (see Section 8.4.4.2.1 and Table 8-2).

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported outcome (PRO) scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study.

The G1T28-02 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 29 months.

Part 1 is expected to be approximately 18 months, assuming 12 months of accrual, 2 weeks for screening, 4.5 months of treatment (assuming 6 cycles), and 1 month of safety follow-up.

Part 2 will begin after the Part 2 dose is identified from the Phase 1b dose-finding portion of Part 1 and the Phase 2a expansion portion of Part 1 has completed enrollment, which is expected to occur approximately 12 months after Part 1 begins. Part 2 is expected to be approximately 17 months, assuming 11 months of accrual, 2 weeks of screening, 4.5 months of treatment (assuming 6 cycles), and 1 month of safety follow-up.

The Survival Follow-up Phase of the study will continue until at least 50% of the randomized patients in Part 2 have died.

6.1.4. Safety Assessments

Safety assessments will include monitoring of AEs, vital signs measurements, physical examinations, ECGs, and clinical laboratory studies as described in Section 11.3. Safety surveillance reporting of AEs commences at the time that informed consent is obtained and continues through the Post-Treatment Visit.

6.1.5. Tumor Assessment

For tumor assessment, all sites of disease should be assessed radiologically according to RECIST, Version 1.1 using computed tomography (CT) or magnetic resonance imaging (MRI) at screening; after every even cycle, 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. Assessments should be performed within 7 days

of starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (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. Patients with a confirmed PR should also consider PCI after completion of chemotherapy based on the investigator's judgment (see Section 8.8). 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 positron emission tomography (PET) is used, it should also be accompanied by spiral CT or MRI. Tumor assessment is further described in Section 11.5.

7. STUDY POPULATION

7.1. Selection of Patients

Overall, up to 110 patients will be enrolled in the study.

In Part 1, approximately 40 patients will be enrolled, assuming up to 3 cohorts. Cohorts will consist of 6 patients each in the Phase 1b dose-finding portion of Part 1 and up to 18 patients in the Phase 2a expansion portion of Part 1 at the selected dose to be used in Part 2. Additional patients may be enrolled in the Phase 1b dose-finding portion of Part 1 if more than 1 cohort is enrolled.

In Part 2, 70 patients will be randomly assigned (1:1 ratio) to 1 of 2 groups: G1T28 administered IV with E/P therapy (Group 1) or placebo administered IV with E/P therapy (Group 2).

The study will be conducted at up to 80 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 disease
4. At least 1 target lesion that is unirradiated and measurable by RECIST, Version 1.1 (Eisenhauer 2009)
5. Hemoglobin ≥ 9.0 g/dL
6. Absolute neutrophil count ≥ 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/min (by Cockcroft-Gault formula [Cockcroft and Gault 1976]); creatinine clearance calculated from an isotopic method or a 24-hour urine collection may be used instead of an estimated GFR by the Cockcroft-Gault formula
9. Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
10. AST and ALT ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases
11. Serum albumin ≥ 3 g/dL

12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

13. Predicted life expectancy of ≥ 3 months

14. Contraception:

    a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and at baseline. Females must be either postmenopausal, surgically sterile, or using an acceptable method of contraception. Acceptable surgical sterilization techniques are hysterectomy, bilateral tubal ligation with surgery at least 6 months prior to dosing, and bilateral oophorectomy, with surgery at least 2 months prior to dosing. Acceptable methods of contraception are an intrauterine device, contraceptive implant, oral contraceptive (stable dose of the same hormonal contraceptive product for at least 3 months prior to dosing), a vasectomized partner, and a barrier method (condom or diaphragm) during the study and for 3 months after discontinuation of treatment
    b. For males: Patients with female partner of childbearing potential must agree to use a highly effective form of birth control, which entails the use of oral, injected, or implanted hormonal methods of contraception or an intrauterine device/system by the female partner, in combination with a barrier method (eg, condom, diaphragm, cervical cap) during the study and for 3 months after discontinuation of treatment, and will also refrain from sperm donation for 3 months following completion of the study

15. Able to understand and sign an informed consent

7.1.2. Exclusion Criteria

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

1. Prior chemotherapy for limited or extensive-stage SCLC

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

3. History of other malignancies, except for the following: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated a) in situ carcinoma of the uterine cervix, b) prostate cancer, or c) superficial bladder cancer; or (3) other curatively treated solid tumor with no evidence of disease for ≥ 3 years

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

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

6. Serious active infection

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

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

9. Known human immunodeficiency virus (HIV), known hepatitis B virus (HBV), or known hepatitis C virus (HCV) positive that is symptomatic or requiring active therapy

10. Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response)

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

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

13. Hypersensitivity to cisplatin or other platinum-containing compounds, or mannitol

14. Legal incapacity or limited legal capacity

15. 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

The initial group of patients in Part 1 of the study will receive G1T28 200 mg/m^2 administered IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. All dose escalation/de-escalation decisions and additional cohorts of patients to be enrolled in the Phase 1b dose-finding portion of Part 1, if any, will be based on Cycle 1 safety and available PK data (see Section 6.1.1). If the G1T28 dose level for a subsequent cohort is adjusted by the SMC, the SMC may also recommend that all patients currently receiving G1T28 in combination with E/P therapy should have their G1T28 dose adjusted accordingly, starting with their next scheduled cycle.

Patients enrolled to the Phase 2a expansion portion of Part 1 and Part 2 will receive the dose of G1T28 derived from the Phase 1b dose-finding portion of Part 1 or placebo administered IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. There will be no intrapatient dose modifications of G1T28 in the Phase 2a expansion portion of Part 1 and Part 2 of the study.

Patients will receive standard E/P chemotherapy in 21-day cycles. The carboplatin dose will be calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1, and 100 mg/m^2 etoposide will be administered IV daily on Days 1, 2, and 3 of each 21-day cycle.

The interval between doses of G1T28 or placebo on successive days should not be greater than 28 hours. The interval between the dose of G1T28 or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours.

G1T28 or placebo will only be administered with E/P therapy. If administration of E/P therapy is discontinued, G1T28 or placebo will also be discontinued.

Chemotherapy cannot be administered until after completion of the G1T28 or placebo infusion. If the second or third dose of G1T28 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 8.4.4.1).

Study drug administration will continue until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator (eg, after completing 6 cycles), whichever occurs first. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities or for up to a 1 week delay for administrative reasons, for a maximum total delay of up to 2 weeks. If the subsequent 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, as well as on the actual first dosing day of the next cycle.

Patients should meet the laboratory parameter requirements outlined in Section 10.4 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.

8.2. Investigational Products

8.2.1. Identity

8.2.1.1. G1T28

G1T28 is supplied as a single-use, sterile powder with 40 or 100 mg G1T28 in each 10-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 2).

8.2.2. Packaging and Labeling

8.2.2.1. G1T28

G1T28 sterile powder is manufactured and packaged by University of Iowa Pharmaceuticals, Iowa City, Iowa, United States of America.

Individual vials of G1T28 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 2).

8.2.3. Storage

8.2.3.1. G1T28

The G1T28 sterile powder 40-mg/10 mL or 100-mg/10 mL vial should be stored refrigerated at 2°C to 8°C.

Stability data for the current formulation of G1T28 sterile powder 40-mg/10 mL vial demonstrates satisfactory stability for up to 6 months at 5°C and 25°C/60% relative humidity (RH). Based on these data, stability is expected to exceed 18 months at refrigerated storage conditions.

Stability data for the current formulation of G1T28 sterile powder 100-mg/10 mL vial demonstrates satisfactory stability for up to 1 month at 40°C/75% RH. Based on these data, stability is expected to exceed 12 months at refrigerated storage conditions.

Study drugs will be stored in a locked refrigerator under applicable storage conditions at the site and only the pharmacist/designee and designated personnel will have access to the study drugs.

8.2.3.2. Placebo

The placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% will be stored identically to G1T28 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 2).

8.2.4. Procedure for Dispensing

Dispensing instructions, including instructions for masking the G1T28 or placebo infusion bags, 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. Once a patient is determined eligible, ie, meets all inclusion/exclusion criteria, an enrollment number will be assigned by an interactive web-response system (IWRS).

Part 1 of the study (dose-finding and expansion cohorts) is open-label and there will be no randomization.

Part 2 is randomized and blinded. Patients meeting all inclusion and exclusion criteria in Part 2 will be randomized 1:1 to receive G1T28 or placebo as described in Section 8.5. Each patient will be assigned a unique randomization number, which will not be reused.

8.4. Dose, Dosing Regimen, and Route

8.4.1. G1T28

The starting dose level for the Phase 1b dose-finding portion of Part 1 will be 200 mg/m^2, which is derived from the G1T28-1-01 study, a Phase 1a safety, PK, and pharmacodynamic study of G1T28 in healthy male and female subjects. See Section 6.1 for possible dose escalation/de-escalation decisions based on safety and available PK data.

G1T28 diluted in 250 mL of D5W or sodium chloride solution 0.9% is to be administered by IV infusion over 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 G1T28 vials are detailed in the Pharmacy Manual.

The interval between doses of G1T28 on successive days should not be greater than 28 hours. G1T28 will only be administered with E/P therapy. If administration of E/P therapy is discontinued, G1T28 will also be discontinued.

8.4.2. Placebo

The placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% will be administered over 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 discontinued, placebo will also be discontinued.

8.4.3. Etoposide and Carboplatin

Etoposide and carboplatin will be administered IV in accordance with the prescribing information (see Appendix 2) 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 G1T28 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 G1T28 or placebo infusion. If the second or third dose of G1T28 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 8.4.4.1).

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 minutes. The Calvert formula is as follows:

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

Because each patient's estimated GFR will 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 150 mL/min for patients with normal renal function (ie, maximum carboplatin dose = target AUC of 5 mg•min/mL × 150 mL/min = 750 mg).

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

8.4.4. **Dose Modifications**

8.4.4.1. G1T28

To ensure the greatest level of safety when G1T28 is coadministered with chemotherapeutic agents, the magnitude and duration of G1T28-induced HSPC arrest was simulated using a PK/PD model and verified by performing bone marrow cell cycle analysis before or after administration of G1T28 IV at 192 mg/m^2 to different groups of human subjects in the Phase 1a Study G1T28-1-01. G1T28 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 4.2). 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. **To minimize this risk, the dose of G1T28 will not be modified and will remain at 200 mg/m^2 (or the adjusted dose from the Phase 1b dose-finding portion of Part 1 as described in Section 6.1.1) throughout the study**.

8.4.4.2. Modification of Etoposide and Carboplatin Dosing

Patients should meet the laboratory parameter requirements outlined in Section 10.4 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 E/P therapy may be delayed by no more than 2 weeks to allow recovery from toxicity due to the chemotherapy agents. A treatment delay of > 2 weeks due to toxicity will lead to discontinuation of E/P therapy.

No more than 2 dose reductions 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 E/P therapy. Under this circumstance, administration of G1T28 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 Cycle 2 and Beyond

In order to start Cycle 2 and subsequent 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 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 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 2006).	No change. Use G-CSF with subsequent cycles. Refer to ASCO guidelines (Smith 2006).
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

Absolute Neutrophil Count Nadir	Etoposide	Carboplatin
Grade 3 (without fever)	No Change	No change
Grade 4 for ≥ 7 days (without fever)		
First episode	No change. Use G-CSF with subsequent cycles. Refer to the ASCO guidelines (Smith 2006).	No change. Use G-CSF with subsequent cycles. Refer to ASCO guidelines (Smith 2006).
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 2006).	No change. Use G-CSF with subsequent cycles. Refer to ASCO guidelines (Smith 2006).
Second episode	First dose reduction	First dose reduction
Third episode	Second dose reduction	Second dose reduction
Fourth episode	Discontinue drug	Discontinue drug

G-CSF = granulocyte colony-stimulating factor

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 or ≥ Grade 3 with bleeding		
First episode	First dose reduction	First dose reduction
Second episode	Second dose reduction	Second dose reduction
Third episode	Discontinue drug	Discontinue drug

Colony Stimulating Factors

Patients will not receive colony stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF]; granulocyte-macrophage colony-stimulating factor [GM-CSF]) or erythropoiesis stimulating agents (ESAs) during Cycle 1 (ie, prior to the actual Cycle 2 Day 1 dosing visit). Subsequent use will be based on toxicities as outlined above. Please also refer to the ASCO guidelines (Smith 2006) for neutropenia. For a hemoglobin level < 9.0 g/dL or symptomatic anemia, ESAs may be used per the current prescribing information.

When indicated, as outlined above in Table 8-2 and Table 8-3, either filgrastim or pegfilgrastim may be used per the prescribing information detailed in the package inserts (see Appendix 3). 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.

When indicated, epoetin alfa or darbepoetin alfa may be used to treat patients with anemia per the prescribing information detailed in the package inserts (see Appendix 4).

8.4.4.2.1. Dose Modifications for Nonhematologic Toxicity

Hepatic Toxicity

The following dose adjustments for E/P 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[a]	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

a If baseline is Grade 2 in the presence of liver metastases, an increase of 1 Grade will result in the first dose level reduction

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. 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), all study treatments 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, treatment should be resumed at dose level -1; for the third occurrence, the dose should be reduced to dose level -2. A fourth occurrence will result in discontinuation of 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, all study treatments 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 E/P therapy.

8.5. Randomization and Blinding

Part 1 is open-label and no randomization or blinding will be required.

Part 2 is randomized and blinded. Patients meeting all inclusion and exclusion criteria in Part 2 will be randomized 1:1 to receive G1T28 or placebo by an IWRS according to a randomization schedule generated by an unblinded statistician. Randomization of patients will be performed centrally and will be stratified by ECOG performance status (0 to 1 versus 2). 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.

Concomitant radiation therapy treatment for SCLC will be regarded as disease progression, and is not permitted while on this study.

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 Cycle 1 will not be permitted (ie, no growth factors should be used prior to the actual Cycle 2 Day 1 dosing visit).** However, hematopoietic growth factors may be utilized in subsequent cycles at the investigator's discretion as stated in Section 8.4.4.2. To reduce potential immune system interactions, the use of dexamethasone as an antiemetic should be minimized where possible.

G1T28 is a time-dependent inhibitor of CYP3A4 and is a substrate for CYP3A4. G1T28 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 G1T28 (Section 4.3.2).

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

G1T28 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 4.3.2).

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

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 (Smith 2006).

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 chemotherapy. Patients with a confirmed PR should also consider PCI after completion of chemotherapy based on the investigator's judgment.

8.9. Treatment Compliance

The investigator or designee will dispense the study medication, via an unblinded pharmacist/designee, only for use by patients enrolled in the study as described in this protocol. The study drug is not to be used for reasons other than those described in this protocol. The investigator or other study staff will supervise each dose of the study drug administered in the clinic. The clinical study site will maintain records of study drug receipt, preparation, and dispensing, including the applicable lot numbers; patient's height, body weight, and BSA; date and time of the start and end of each G1T28 or placebo, etoposide, and carboplatin 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.

Table 9-1 Schedule of Assessments

	Screen-ing	Enroll	Cycle 1 and Every Odd Cycle[a] (21 days)						Cycle 2 and Every Even Cycle[a] (21 days)						Last Cycle	Post-Treatment Visit[b]	Survival Follow-up[c]
Cycle Day	**-14**	**-3 to 1**	**1**	**2**	**3**	**8**	**10**	**15**	**1**	**2**	**3**	**8**	**10**	**15**	**22**		
Informed Consent[d]	X																
Demographics	X																
Medical History[e]	X																
Eligibility Eval.	X	X															
Performance Status	X		X						X							X	
Physical Exam	X		X						X							X	
Height, Weight & Vital Signs[f]	X		X						X							X	
Clinical Chemistry	X		X[g]			X		X	X[g]			X		X		X	
Hematology	X		X[h]		X	X	X	X	X[h]		X	X	X	X	X	X	X[i]
Urinalysis	X		X[g]						X[g]							X	
ECG	X		X[j]		X[j]											X	
Pregnancy test[k]	X		X						X								
Randomization[l]		X															
Tumor Assessment[m]	X[m2]													X		X[m1,m2]	X[m1]
Tumor Testing[n]		X															
PK[o]			X		X												
G1T28 or Placebo[p]			X	X	X				X	X	X						
Carboplatin			X						X								
Etoposide			X	X	X				X	X	X						
FACT-L and FACT-An[q]			X				X		X				X			X	
Immunologic Marker[r]			X													X	X
AEs[s]	X	X								X							
Con. Medications	X	X								X							
Survival Follow-up[c]		X															X

AE = adverse event; ECG = electrocardiogram; FACT-AN = Functional Assessment of Cancer Therapy – Anemia quality of life instrument; FACT-L = Functional Assessment of Cancer Therapy – Lung quality of life instrument; PRO = patient reported outcome; Eval. = evaluation; PK = pharmacokinetics

a G1T28 or placebo + E/P therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). The tumor should be assessed after every even cycle. Assessments should be performed within 7 days of starting the subsequent cycle.

b Patients will return to the study center for a Post-Treatment Visit at 30 days (+ 3 days) after the last dose of study drug.

c 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 until at least 50% of the patients in Part 2 have died. Any anticancer therapies used will be collected. In addition, blood samples for hematology and immunologic marker assessment will be collected at 60 ± 7 days after the Post-Treatment Visit for patients in Part 2 only.

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

e 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.

f Height will only be measured at the screening visit. Body surface area calculation (based on actual body weight) will be completed on Day 1 of each cycle and vital signs obtained immediately before and after G1T28 or placebo and E/P infusions. Vitals only need to be taken once between infusions.

g Clinical chemistry will be obtained (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]); see Section 11.3.2. Clinical chemistry and urine analysis may be obtained up to 72 hours prior to the first dose of each cycle of G1T28 or placebo + E/P therapy.

h Hematology will be obtained (hemoglobin, hematocrit, WBCs with differential, and platelet counts); see Section 11.3.2. Hematology may be obtained up to 24 hours prior to first dose of each cycle of G1T28/placebo + EP therapy.

i In Part 2 only, hematology will be collected at 60 days after the Post-Treatment Visit.

j Patients participating in the Phase 1b dose-finding portion of Part 1 of the study, who have PK samples obtained, will have ECGs completed at the following time points on Days 1 and 3 of Cycle 1: predose, end of infusion (EOI) of G1T28, 2 hours (± 10 minutes) after the start of G1T28, and 6.5 hours (± 15 minutes) after the start of G1T28. The 2-hour ECG will be completed once the etoposide infusion is complete.

k For female patients of childbearing potential, serum ß-hCG at screening; serum or urine ß-hCG obtained up to 72 hours prior to Day 1 dose of G1T28 or placebo + E/P chemotherapy in each cycle.

l For patients enrolled in Part 2, randomization is to be done within 3 days prior to first dose of G1T28 or placebo + E/P chemotherapy, following confirmation that the patient is eligible for the study.

m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle, 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.

m1: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks). 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.

m2: Brain scans with contrast (by CT or MRI) to be obtained with tumor assessment at screening (within 28 days of dosing) and at the Post-Treatment Visit

n Send archived tumor samples to a central pathology laboratory to confirm the diagnosis of SCLC. Available tissue after confirming the diagnosis of SCLC will be banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the CDK4/6 pathway. If central pathology review does not confirm SCLC diagnosis, the patient may be withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor. This should be done as soon as possible after a patient has enrolled in the study.

o Patients enrolled in Cohort 1 of the Phase 1b dose-finding portion of Part 1 will have G1T28, etoposide, and carboplatin PK samples collected on Days 1 and 3 (as applicable) of Cycle 1 at the time points specified in Section 11.2. Collection of PK blood samples from patients enrolled in additional cohorts of the Phase 1b dose-finding portion of Part 1 is optional.

p G1T28 or placebo will be administered as an IV infusion in 250 mL of D5W or sodium chloride solution 0.9% over 30 minutes prior to E/P chemotherapy on Days 1 to 3 of every cycle (see Section 8.1). If there is any volume remaining in the G1T28 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 G1T28 or placebo on successive days should not be greater than 28 hours. The interval between the dose of G1T28 or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours. G1T28 or placebo will only be administered with E/P therapy. If administration of E/P therapy is discontinued, G1T28 or placebo should also be discontinued. Chemotherapy cannot be administered until after completion of the G1T28 or placebo infusion. If the second or third dose of G1T28 in any given cycle is not administered for any reason, do not administer the dose of etoposide or carboplatin chemotherapy on that day (see Section 8.1). After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported outcome (PRO) scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study.

q Patient-reported outcomes should be completed at Days 1 and 10 of each cycle and at the Post-Treatment Visit. If a cycle is delayed, the patient should still complete the PRO on the scheduled Day 1 of the next cycle, as well as the actual first dosing day of the next cycle of G1T28 or placebo + E/P therapy. Patient-reported outcomes may be obtained up to 24 hours prior to the first dose of each cycle of G1T28 or placebo + E/P therapy.

r In Part 2 only, peripheral blood samples for immunologic marker assessment will be collected at predose on Day 1 of Cycles 1, 3, and 5; at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

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

10. SCHEDULE OF STUDY PROCEDURES

Study procedures are summarized across all study visits within the schedule of assessments (Table 9-1). Both Parts 1 and 2 of the study will follow the same study schedule, except where noted below.

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
- Clinical chemistry, hematology, and urinalysis tests
- Electrocardiogram
- Pregnancy test
- Tumor assessment (by CT scan or MRI; see details in Section 11.5.1); 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.

Adverse events and concomitant medications will be monitored continuously from the time of informed consent through the Post-Treatment Visit.

10.2. Enrollment

Eligibility will be determined prior to enrollment, randomization (Part 2), and the start of study treatment. Eligible patients will be instructed on all protocol requirements, including any restrictions on concomitant medication usage.

For Part 2 of the study, randomization will be performed within 3 days of the first dose of G1T28 or placebo + E/P chemotherapy, following confirmation that the patient is eligible for the study.

Archived tumor samples must be sent to a central pathology laboratory to confirm the diagnosis of SCLC. Available tissue after confirming the diagnosis of SCLC will be banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the CDK4/6 pathway (see Section 11.4). This should be done as soon as possible after a patient

has enrolled in the study. If central pathology review does not confirm SCLC diagnosis, the patient may be withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor. For additional guidance regarding the shipment of samples to the central pathology laboratory, please refer to the Laboratory Manual.

10.3. Cycle 1

Adverse events and concomitant medications will be monitored throughout the study. Safety surveillance reporting of AEs commences at the time informed consent and continues through the Post-Treatment Visit.

Cycle 1 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). **For the Phase 1b dose-finding portion of Part 1, Cycle 1 only**, the clinical chemistry and hematology results may be reviewed prior to or after dosing, depending on the availability of the lab report. For Day 1 of all subsequent cycles, the clinical chemistry and hematology results should be reviewed before dosing.
- Electrocardiogram (as applicable and optional after Cohort 1, predose, **Cycle 1 in the Phase 1b dose-finding portion of Part 1 only**)
- Plasma PK sample (as applicable and optional after Cohort 1, predose, **Cycle 1 in the Phase 1b dose-finding portion of Part 1 only**)
- Pregnancy test (note: may be obtained up to 72 hours prior to the first dose of each cycle)
- Functional Assessment of Cancer Therapy – Lung quality of life (QOL) instrument (FACT-L) and Functional Assessment of Cancer Therapy –Anemia QOL instrument (FACT-An) Questionnaires
- Immunologic marker blood sample collection (predose, **Part 2 only**)

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

Patients that still meet all of the eligibility criteria will begin treatment Cycle 1. The first dose of study treatments (G1T28 or placebo + E/P chemotherapy) 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 immediately before and after G1T28 or placebo infusion, and etoposide and carboplatin infusions; only needed once between infusions)
- Electrocardiogram (as applicable, end of infusion [EOI] of G1T28, 2 hours (± 10 minutes) after the start of G1T28, and 6.5 hours (± 15 minutes) after the start of

G1T28, **Cycle 1 in the Phase 1b dose-finding portion of Part 1 only**). The 2-hour ECG will be completed once the etoposide infusion is complete.
- Plasma PK samples (as applicable and optional after Cohort 1, postdose samples as described in Section 11.2, **Cycle 1 in the Phase 1b dose-finding portion of Part 1 only**)

Cycle 1 Days 2, 3, 8, 10, and 15

All procedures and assessments to be conducted during Cycle 1 Days 2, 3, 8, 10, 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) will be notified if the frequency is reduced.

At Day 2 and Day 3, study treatments (G1T28 or placebo + etoposide) will be administered (as described in Section 8.1).

At Day 3 in Cycle 1 of the Phase 1b dose-finding portion of Part 1 only, the following additional assessments will be performed:

- Electrocardiogram (as applicable, predose, EOI, and 2 hours (± 10 minutes) and 6.5 hours (± 15 minutes) after the start of G1T28)
- Plasma PK sample (as applicable and optional after Cohort 1, predose and postdose samples as described in Section 11.2)

10.4. Cycle 2

Adverse events and concomitant medications will be monitored throughout the study. Safety surveillance reporting of AEs commences at the time of informed consent and continues through the Post-Treatment Visit.

Cycle 2 Day 1

Patients will return to the study center on 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 (calculate BSA)
- 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)
- Pregnancy test (note: may be obtained up to 72 hours prior to the first dose of each cycle)
- FACT-L and FACT-An Questionnaires

Vital signs should be obtained immediately before and after G1T28 or placebo, etoposide, and carboplatin infusions; only once between infusions.

In order to start Cycle 2 and subsequent cycles as scheduled, on Day 1 of the cycle, patients must have an ANC ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 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 2 weeks is permitted to allow recovery from any toxicity in order to meet the continuation criteria for organ function. If the patient meets the criteria for starting the subsequent cycle as stated in protocol Section 6.1.3, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). 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 G1T28 or placebo + E/P therapy.

A patient will be discontinued from the study if recovery from any toxicity, in order to meet the continuation criteria for organ function, and any delay for administrative reasons requires a total delay of > 2 weeks.

Study treatments (G1T28 or placebo + E/P chemotherapy) will be administered as described in Section 8.1.

Cycle 2 Days 2, 3, 8, 10, and 15

All procedures and assessments to be conducted during Cycle 2 Days 2, 3, 8, 10, 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.

For Cycle 2 Day 2 and Day 3, study treatments (G1T28 or placebo + etoposide) will be administered as described in Section 8.1.

For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle, 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. 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.

10.5. Cycles 3, 4, and Subsequent Cycles

Procedures and assessments to be performed during Cycle 3 and all subsequent odd numbered cycles are similar to Cycle 1 (see Section 10.3 and Table 9-1).

Procedures and assessments to be performed during Cycle 4 and all subsequent even numbered cycles are similar to Cycle 2 (see Section 10.4 and Table 9-1).

In order to start each subsequent cycle as scheduled on the first day of the cycle, patients must have an ANC ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 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 each subsequent cycle are outlined in Table 8-2. A delay of up to 2 weeks is permitted to allow recovery from any toxicity in order to meet the continuation criteria for organ function. If the patient meets the criteria for starting the subsequent cycle as stated in protocol Section 6.1.3, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). A patient will be discontinued from the study if recovery from any toxicity, in order to meet the continuation criteria for organ function, and any delay for administrative reasons requires a total delay of > 2 weeks.

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the patient-reported outcome (PRO) scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study, which is to continue until at least 50% of randomized patients in Part 2 have died.

10.6. Post-Treatment Visit

Patients will return to the study center for a Post-Treatment Visit within 30 days from the last dose (+ 3 days). The following procedures will be performed at this visit:

- ECOG performance status evaluation
- Physical examination
- Weight and vital signs measurements
- Clinical chemistry, hematology, and urinalysis tests
- Electrocardiogram
- Tumor assessment (obtain tumor assessment by CT scan or MRI for patients who have not progressed at the time of study drug discontinuation [may be performed within 4 weeks]); see details in Section 11.5.1)
- 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])
- FACT-L and FACT-An Questionnaires
- Immunologic markers blood sample collection (**Part 2 only**)

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.

After completing the Post-Treatment Visit, 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 50% of the patients randomized to Part 2 of 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

The following additional information will be collected at 60 ± 7 days after the Post-Treatment Visit (**Part 2 only**):

- Immunologic markers blood sample collection
- Hematology sample collection

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, including the patient-reported outcome (PRO) scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study, which is to continue until at least 50% of randomized patients in Part 2 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. Efficacy Assessments

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

The toxicity of G1T28 administered IV with E/P therapy will be assessed using the NCI CTCAE, Version 4.03.

11.2. Pharmacokinetic Assessments

In the Phase 1b dose-finding portion of Part 1 of the study, serial blood samples (5-mL samples) will be collected for measurement of G1T28, etoposide, and carboplatin concentrations in plasma at the time points outlined below and in Table 9-1. 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 G1T28, etoposide, and carboplatin using a validated method. Any remaining sample may be stored long term for the future analysis of G1T28 drug metabolites.

Phase 1b Dose-Finding Portion of Part 1: Cycle 1 Day 1

Blood samples will be collected at the following time points on Cycle 1 Day 1 for all patients enrolled in Cohort 1 of the Phase 1b dose-finding portion of Part 1 of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (end of infusion [EOI] of G1T28), 1 (EOI of carboplatin), 1.5, 2 (EOI of etoposide), 2.5, 3, 4.5, 6.5, 8.5 (optional time point, if approved by the sponsor in advance), and 24.5 hours postdose (relative to the start of G1T28 infusion). Collection of PK blood samples in additional cohorts of the Phase 1b dose-finding portion of Part 1 is optional. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. The EOI samples for G1T28, 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 2.5 hours after the end of G1T28 infusion. A ± 10-minute time window will be allowed for samples collected between the following time points: 3 to 8.5 hours after the end of G1T28 infusion. A ± 1-hour time window will be allowed for the 24.5 hours after the end of G1T28 infusion time point. The actual time of blood sample collection should be documented in the eCRF. The Cycle 1 Day 1 sampling scheme is summarized in Table 11-1.

Table 11-1 Day 1 of Cycle 1 Blood Sampling Scheme Based on Predicted Administration Times of G1T28, Carboplatin, and Etoposide

Sample	1	2	3	4	5	6	7	8	9	10	11
Sample Time (h)	0 (Predose[a])	0.5[b] (G1T28 EOI)	1 (Carbo EOI)	1.5	2 (Etop EOI)	2.5	3	4.5	6.5	8.5 (optional[c])	24.5

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

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

a Predose is defined as prior to dosing of G1T28.

b The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI.

c 8.5 hour sample (optional time point, if approved by the sponsor in advance)

Phase 1b Dose-Finding Portion of Part 1: Cycle 1 Day 3

Blood samples will be collected at the following time points on Cycle 1 Day 3 for all Cohort 1 patients enrolled in the Phase 1b dose-finding portion of Part 1 of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (EOI of G1T28), 1, 1.5 (EOI of etoposide), 2, 2.5, 3.5, 4.5, 6.5, 8.5 (optional time point, if approved by the sponsor in advance), and 24.5 hours postdose (relative to the start of G1T28 infusion). Collection of PK blood samples in additional cohorts of the Phase 1b dose-finding portion of Part 1 is optional. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. The EOI samples for G1T28 and etoposide must be drawn after completing infusion of the drugs and the actual times at which the samples were drawn should be documented. Time window parameters noted above for Cycle 1 Day 1 also apply to Cycle 1 Day 3. The Cycle 1 Day 3 sampling scheme is summarized in Table 11-2.

Table 11-2 Day 3 of Cycle 1 Blood Sampling Scheme Based on Predicted Administration Times of G1T28 and Etoposide

Sample	1	2	3	4	5	6	7	8	9	10	11
Sample Time (h)	0 (Predose[a])	0.5[b] (G1T28 EOI)	1	1.5 (Etop EOI)	2	2.5	3.5	4.5	6.5	8.5 (optional[c])	24.5

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

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

a Predose is defined as prior to dosing of G1T28.

b The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI.

c 8.5 hour sample (optional time point, if approved by the sponsor in advance)

Pharmacokinetic Parameters

Pharmacokinetic parameters to be derived from G1T28, etoposide, and carboplatin plasma concentration-time data are presented in Table 11-3.

Table 11-3 Pharmacokinetic Parameters

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

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

11.3. Safety Assessments

Safety evaluations will be conducted at baseline and throughout the study. Safety evaluations will include monitoring of AEs, vital signs measurements, physical examinations, ECGs, clinical laboratory studies, infusion-related reactions, tumor response based on RECIST, Version 1.1 (see Section 11.5), PFS, and overall survival.

The toxicity of G1T28 administered IV with chemotherapy will be assessed by the investigators using the NCI CTCAE, Version 4.03.

11.3.1. **Adverse Events and Serious Adverse Events**

11.3.1.1. 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 Investigator Brochure 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.

11.3.1.2. 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 11.3.1.9) is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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

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

11.3.1.3. Assessment of the Severity of Adverse Events

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

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

The investigator will determine the assessment of the causal relationship of the AE to the study drug. 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.

11.3.1.5. 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

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

Safety surveillance reporting of AEs commences at the time of informed consent and continues through 30 days after last dose of study drug (eg, the Post-Treatment Visit).

11.3.1.7. Documentation of Adverse Events and Serious Adverse Events

All AEs will be documented in the appropriate section of the eCRF. The CTCAE, Version 4.03 grading scale referenced in Appendix 1 is provided to assist in categorizing and grading AEs. All SAEs (see Section 11.3.1.2) 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

11.3.1.8. Adverse Event Coding

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

11.3.1.9. Reporting of Serious Adverse Events

The reporting period for SAEs begins from the time of informed consent through and including 30 calendar days after the last administration of G1T28 or placebo + E/P therapy. Any SAE that is thought to be related to the study drug and that occurs after the reporting period must be reported **within 24 hours** of discovery of the SAE.

All SAEs must be entered into the eCRF and the initial SAE form should be completed and sent to the safety team within 24 hours of first knowledge of the event by the study personnel. The contact information for the safety team will be provided in the Site Reference Manual.

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.

11.3.1.10. Follow-up of Adverse Events

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

11.3.1.11. Regulatory Aspects of Adverse Event Reporting

Unexpected serious adverse reactions are subject to expedited reporting to the Food and Drug Administration (FDA), the Medicines and Healthcare Products Regulatory Agency (MHRA), and European National Competent Authorities in other Member States, if applicable, in an expedited time frame in compliance with current legislation. All SAEs must be entered into the eCRF and the initial SAE form should be completed 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. The contact information for the medical monitor and safety team will be provided in the Site Reference Manual.

G1 Therapeutics, or their designee, is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA, MHRA, and European National Competent Authorities in other Member States, if applicable, in an expedited time frame in compliance with current legislation. Unexpected serious adverse 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 independent ethics committee.

11.3.1.12. Handling of Overdoses and Toxicity

No information on treatment of overdose of G1T28 is currently available. General supportive measures should be used as appropriate.

11.3.1.13. Reporting of Pregnancies

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

Each pregnancy in a study patient or partner of a study patient must be reported to the sponsor within 24 hours of learning of its occurrence. 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.

The avoidance of pregnancy or fathering a child (including sperm donation) is suggested for 3 months following the discontinuation of study drug. No information is currently available regarding the effects of G1T28 on fertility, gestation, or subsequent child development.

11.3.2. **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, hematocrit, white blood cells [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, sodium, and BUN)
- 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. The investigator will review the laboratory report within 24 hours (except during clinic holidays, when review will be performed within 72 hours) after receipt of the results and indicate the clinical significance of all abnormal

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

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

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

11.3.3. 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, and respiration rate will be measured with the patient. Blood pressure should be assessed after 5 minutes of rest.

11.3.4. 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.

11.3.5. Electrocardiogram Assessments

Standard 12-lead ECGs will be performed as outlined in Table 9-1. Obtain ECGs in the Phase 1b dose-finding portion of Part 1 only if PK samples are also obtained. Patients should rest for 5 minutes prior to each ECG assessment.

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

11.3.6. 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.

11.4. Central Pathology Review to Confirm Diagnosis of SCLC

Archived tumor samples should be sent to the central pathology laboratory as soon as possible after enrollment to confirm the diagnosis of SCLC. Available tissue after confirming the diagnosis of SCLC will be banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the CDK4/6 pathway (as described in the Laboratory Manual). If central pathology review does not confirm SCLC diagnosis, the patient may be withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor. Archived tumor samples may also be used for future genomic testing related to the mechanism of drug action.

11.5. Tumor Response

11.5.1. Tumor Assessments

For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle, 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. Assessments should be performed within 7 days of starting the subsequent cycle. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. For 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 (see Section 8.8). 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, Version 1.1 guidelines (Eisenhauer 2009) for tumor assessments.

11.5.2. Tumor Lesions: Identification and Follow-up

11.5.2.1. Measurable Lesions

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

11.5.2.2. Nonmeasurable Lesions

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

11.5.2.3. New Lesions

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

11.5.3. Definitions of Tumor Response and Disease Progression

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

11.5.3.1. Evaluation of Target Lesion Response

- **Complete response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- **Partial response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the 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.

11.5.3.2. Evaluation of Nontarget Lesions

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

11.5.3.3. Evaluation of Overall Response

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

Table 11-4 describes the evaluation of overall response at each time point based on target and nontarget lesion responses at each time point, as well as the appearance of new lesions. The

best overall response is the best response recorded from the start of the treatment until disease progression. Confirmation of CR and PR is required as described in Sections 11.5.3.1 and 11.5.3.2.

Table 11-4 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)

11.6. 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, Day 10 of each cycle (may be administered by phone if the patient is unable to return to clinic), 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.

11.7. Immunologic Markers

The addition of G1T28 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 G1T28 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 progression-free and overall survival (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. Therefore, to evaluate the impact of G1T28 administration on chemotherapy-induced changes of the immune system, peripheral blood immune subsets will be characterized in patients enrolled into Part 2 of the study. Immunophenotypic changes will be compared between patients receiving E/P therapy plus placebo or G1T28. To assess these changes, peripheral blood will be collected at predose on Day 1 of Cycles 1, 3, and 5; at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

Immunophenotyping

Whole blood samples (15 mL) for immunophenotyping will be obtained from patients enrolled in Part 2. Comprehensive information on the blood sample acquisition, the specific type of collection tubes with anticoagulant, and handling and storage are to be found in the laboratory manual.

11.8. Appropriateness of Measurements

The measures of efficacy, PK, and safety evaluated in this study are based on the mechanism and activity of G1T28, standard types of assessments typically performed in patients with SCLC, and prior clinical observations derived from patients receiving E/P therapy for SCLC. The measurement of tumor response based on the RECIST, Version 1.1 (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
- 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

In the event of study drug discontinuation, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; CBC assessment on Day 22; the Post-Treatment Visit; and the Survival Follow-up Phase of the study. A patient who discontinues study treatment for reasons other than PD will have a CT or MRI scan at the Post-Treatment Visit, if they have not had a scan within the prior 4 weeks.

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

When discontinuation is due to 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)
- If central pathology review does not confirm SCLC diagnosis, the patient may be withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor

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 a separate statistical analysis plan (SAP).

13.1. Sample Size and Power

The sample size for this study is determined by clinical rather than statistical considerations. Up to 40 patients (open-label, dose-finding cohort[s] and an open-label, expansion cohort) will be enrolled in Part 1 of the study and 70 patients will be enrolled in Part 2 of the study (randomized). With 35 patients, the precision for point estimates in each arm is as follows: the 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals are at most the observed proportion ± 0.157. The 95% CI width for continuous endpoints using the t-distribution are the observed mean ± 0.344*standard deviation of the endpoint.

13.2. General Considerations

13.2.1. Analysis Populations/Sets

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

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

A per-protocol (PP) subset may also be used to analyze select endpoints and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PP subset will be finalized and documented prior to unblinding patients in Part 2 of the study.

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. Interim Safety Reviews

A DMC will monitor accumulating safety data according to a charter that defines its roles and responsibilities. The DMC will perform reviews approximately every 4 months during the Treatment Phase of Part 2, 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.

No interim analyses of efficacy are planned.

13.2.2.2. Final Analysis

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

13.2.2.3. End of Study Analysis

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

13.2.3. **General Considerations for Data Analysis**

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

Data will be summarized separately by study part (Part 1 and Part 2). Data from Part 1 will be summarized descriptively by dose level if applicable and overall. Data from Part 2 will be summarized descriptively by treatment group and overall. Treatment differences between treatment groups for Part 2 will be calculated as G1T28 + E/P therapy minus placebo + E/P therapy. Select safety summaries will include combined data from both Part 1 and Part 2 of the study. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, and minimum and maximum values. The descriptive summaries of time to event data will include median, twenty-fifth and seventy-fifth percentiles and standard error. All data will be listed for all patients. Unless specified otherwise, safety summaries will include all collected data, and summaries of efficacy will include data collected through the Treatment Phase.

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

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

Summaries that are based on within-cycle, including changes, events, or findings, will require a clear definition of “end of cycle” that accounts for variable durations in the cycle due to within-cycle dosing delays, delays in subsequent cycle initiation, and incomplete cycles. This will be discussed in the SAP for each applicable endpoint.

Protocol violations will be fully defined and documented before unblinding.

13.3. Baseline and Demographic Characteristics

Demographics and baseline characteristics will be summarized descriptively.

13.4. Efficacy Analysis

13.4.1. Efficacy Endpoints

Unless otherwise stated, the terminology 'hematologic parameters' refers to ANC, lymphocyte, hemoglobin, and platelet counts; the terminology 'hematologic toxicities' refers to neutropenia, lymphopenia, anemia, and thrombocytopenia. Each parameter and toxicity will be evaluated individually, but are described as such to avoid repetition. Hematologic toxicities are assigned based on CTCAE, Version 4.03.

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

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

- Chemotherapy exposure and compliance endpoints:

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

- Other efficacy endpoints:

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

- Exploratory efficacy endpoints:

  - Incidence of Grade 2 or greater nephrotoxicity
  - Incidence of alopecia and mucositis
  - Functional Assessment of Cancer Therapy QOL instrument (FACT) total scale score (general)
  - FACT domain scores (physical, social/family, emotional, and functional well-being)
  - FACT-L total scale score
  - FACT-L lung cancer subscale score
  - FACT-L trial outcome index score
  - FACT-An total scale score
  - FACT-An anemia subscale score
  - FACT-An trial outcome index score
  - Composite hematologic score (this will be specified *a priori* in a SAP)
  - Composite efficacy score (this will be specified *a priori* in a SAP)

13.4.2. **Methods of Analysis for Efficacy Endpoints**

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

13.4.2.1. Analysis of Hematologic Parameter Kinetic Endpoints

Hematologic parameter values will be tabulated with descriptive statistics using absolute counts, change, and percent change values. By-visit tabulations will include values at study

baseline (ie, prior to first dose of study treatment) and each postbaseline visit through all cycles and the Post-Treatment Visit. Changes and percent changes will be calculated at each postbaseline value. Additional tabulations for each cycle of treatment will include predose, nadir, maximum postnadir, and end of cycle values. The change and percent changes from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle values will also be tabulated for each cycle of treatment. Analysis of covariance (ANCOVA) models will be performed for summaries on Part 2, separately at each visit and for each of the following parameters as dependent variables: change from baseline and percent change from baseline. Analysis of covariance models will be performed separately at each cycle and for each of the following parameters as dependent variables: predose (for cycles 2 and onward), nadir, the Post-Treatment Visit counts, change from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle; and percent change from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle. The models will include terms for treatment, ECOG at entry (0 and 1 or 2), and baseline hematologic parameter value. The least square (LS) mean for each treatment group and LS mean difference between treatment groups will be reported. The treatment by ECOG interaction and treatment by baseline hematologic value will be tested. If a significant treatment by ECOG interaction exists, the LS means and LS mean differences will be reported at each level of ECOG at entry. If a treatment by baseline hematologic parameter interaction exists, the LS means and LS mean differences will also be reported at various levels of the covariate (10%, 25%, 50%, 75%, 90%). Two-sided 95% CIs will be constructed around the LS mean differences in treatment groups.

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

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

The proportion of subjects that return to predose values will be summarized by cycle for each hematologic parameter. Percentages for by-cycle summaries will be based on the number of patients treated in the cycle. For tabulations performed based on data collected in Part 2, the difference in rates between treatment groups will be calculated. Two-sided 95% CIs will be constructed around the difference in treatment groups. If there are substantial dose reductions, an incidence rate, adjusting for cumulative exposure, may be reported to account for differing amount of exposure by cycle.

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

13.4.2.2. Analysis of Hematologic Toxicity Endpoints

The number and percentage of patients with Grade 3 and 4 hematologic toxicities at each cycle and overall during the Treatment Phase will be tabulated for each type of hematologic toxicity and across all type of hematologic toxicities. Percentages for by-cycle summaries will be based on the number of patients treated in the cycle. For tabulations performed based on data collected in Part 2, the difference in rates between treatment groups will be calculated. Two-sided 95% CIs will be constructed around the difference in treatment groups. If there are substantial dose reductions, an incidence rate, adjusting for cumulative exposure, may be reported to account for differing amount of exposure by cycle.

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

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

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

13.4.2.3. Analysis of Chemotherapy Exposure and Compliance

The following parameters will be summarized by treatment group and overall: total duration of treatment, total number of cycles received, cumulative dose of E/P therapy received, and number and percentage of patients experiencing one or more dose delay, interruption, and reduction. The following parameters will be summarized for each cycle by treatment group and overall: number and percentage of patients receiving dose at the cycle, experiencing one or more dose delay, interruption, and reduction, and cumulative dose of E/P therapy received. The number and percentage of patients experiencing a treatment cycle delay due to a hematologic toxicity will be summarized by cycle and overall. The number and percentage of

patients discontinuing study treatment due to a hematologic toxicity and cycle of discontinuation will also be summarized.

13.4.2.4. Other Efficacy Endpoints

Infections, RBC and platelet transfusions, systemic antibiotic use, and hematopoietic growth factor use will be summarized with the number and percentage of patients experiencing the event any time during the Treatment Phase of the study. For tabulations performed based on data collected in Part 2, the difference between treatment groups will be calculated and reported as described for the incidence of hematologic endpoints.

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

13.4.2.5. Analysis of Exploratory Efficacy Endpoints

Grade 2 or higher nephrotoxicity, alopecia, and mucositis will be summarized with the number and percentage of patients experiencing the event any time during the Treatment Phase. For tabulations performed based on data collected in Part 2, the difference between treatment groups will be calculated and reported as described for the incidence of hematologic toxicity.

The FACT scores will be calculated per the FACIT version 4 scoring instructions and summarized by visit. The change from baseline in each score will be calculated and presented at each postbaseline visit. Additionally the change from predose to Day 10 and change from predose to end of cycle values will be calculated and presented at each cycle. Analysis of covariance models may be performed for summaries on Part 2, similarly to those described in Section 13.4.2.1. The extreme (best and worst) onstudy values and minimum and maximum change will also be analyzed. The number and percent of patients that have clinically relevant improvements or deteriorations will be summarized.

A single composite endpoint taking into account multiple types of hematologic parameters and other clinically relevant measures is of interest to capture the efficacy of G1T28 + E/P therapy. A composite endpoint will be defined *a priori* in a SAP. Factors such as infection rate, toxicity rates, chemotherapy dose reductions and/or interruptions, incidence of transfusions, incidence of growth factor use, AUC, etc. may be included. The association between composite endpoints and best overall response, overall survival, and PFS may be explored.

Similarly, identifying a composite hematologic score that represents ANC, lymphocytes, platelets, and hemoglobin in a meaningful way will be defined *a priori* in the SAP.

13.5. Safety Analysis

13.5.1. Safety Endpoints

- Incidence of treatment-emergent AEs, SAEs, related AEs, related SAEs, and AEs leading to study drug discontinuation

- Infusion-related reactions
- Vital signs
- Physical examination
- ECG readings
- Clinical hematology, chemistry, and urinalysis results
- Concomitant medications
- Tumor response and best overall response based on RECIST, Version 1.1
- Progression-free survival
- Overall survival

13.5.2. Methods of Analysis for Safety Endpoints

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

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

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

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

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

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

13.6. Exploratory Analyses

Exploratory analyses examining the relationship between hematologic toxicity rates and hematologic changes with study drug exposure will be performed based on rate of chemotherapy interruptions and rate of chemotherapy reductions.

Exploratory analyses will be performed to assess the impact of hematologic kinetics on overall survival, PFS, and best overall response rate. Similarly, exploratory analyses will be performed to assess the impact of cumulative chemotherapy exposure on overall survival, PFS, and best overall response rate. Exploratory analyses will be described in the SAP.

The relationship between G1T28 plasma concentration and hematologic parameter values will be assessed with the Pearson product-moment correlation statistics.

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.

During Part 1 of the study, serial blood samples will be collected on Days 1 and 3 of Cycle 1 to determine G1T28, etoposide, and carboplatin plasma concentrations. 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}, 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. If applicable, G1T28 plasma concentration and PK parameters will also be summarized by dose level.

Exploratory PK modeling and simulations may also be performed.

13.8. Immunologic Markers

To evaluate the impact of G1T28 administration on chemotherapy-induced changes of the immune system, peripheral blood immune subsets will be characterized in patients enrolled into Part 2 of the study. The immunophenotypic change from baseline will be listed and summarized by treatment arm, if data warrant.

Additional exploratory analyses on the relationship between the immunophenotypic changes and safety and efficacy findings may be performed.

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 IRB or a central IRB. 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 prior to initiating the study. Approval must be obtained in writing via a letter identifying the protocol, the date of the IRB meeting, and the date of approval. Any modifications made to the protocol after receipt of the IRB approval must also be submitted by the investigator to the IRB in accordance with local procedures and regulatory requirements. Any updates to the protocol should receive IRB 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, 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 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 must be submitted to the appropriate IRB or independent ethics committee for information in accordance with local requirements. Approval must be awaited 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), except for those changes which would decrease risk to the patient or administrative changes. 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 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 Part 2 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 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 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, electroencephalogram (EEG), X-ray, signed informed consent forms, consultant letters, and patient screening and enrollment 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: Common Terminology Criteria for Adverse Events (CTCAE) –Version 4.03

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

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

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

APPENDIX 2: Package Inserts for Chemotherapy Agents

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

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

APPENDIX 3: Package Inserts for Colony Stimulating Factors

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

Neulasta® (pegfilgrastim) package insert link:
http://pi.amgen.com/united_states/neulasta/neulasta_pi_hcp_english.pdf

APPENDIX 4: Package Inserts for Erythropoiesis Stimulating Agents

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

Epogen® (epoetin alfa) package insert link:
http://pi.amgen.com/united_states/epogen/epogen_pi_hcp_english.pdf