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

**Clinical Study Protocol G1T28-03**
EudraCT # 2016-004611-13

Original Protocol Issue Date: 11 June 2015
Amendment 5 Issue Date: 27 June 2018
Version: 6.0
Investigational Phase: 1b/2a

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

**SPONSOR SIGNATURE PAGE**

## SPONSOR: G1 THERAPEUTICS

I have read and understand the contents of this clinical protocol (Version 6.0) for Study G1T28-03 dated 27 June 2018 and I agree to meet all obligations of the sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the principal investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

**Approved by:**

[redacted] [redacted]

[redacted] Date

[redacted]

G1 Therapeutics

## PROTOCOL SIGNATURE PAGE

**Clinical Study Protocol G1T28-03:** Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Topotecan Chemotherapy

**Original Protocol Issue Date: 11 June 2015**

**Version: 6.0 (Amendment 5), dated 27 June 2018**

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

Principal Investigator:

| | |
|---|---|
| Principal Investigator Signature | Date |
| Principal Investigator Name | Institution |

# 1. TABLE OF CONTENTS

## 1.1. List of In-Text Tables



## 1.2. List of In-Text Figures

# 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 5-FU | 5-fluorouracil |
| 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 |
| CrCl | creatinine clearance |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| D5W | dextrose 5% in water |
| DDI | drug-drug interaction |

| Abbreviation | Definition |
|---|---|
| DLT | dose-limiting toxicity |
| 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 |
| ESA | erythropoietin stimulating agent |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FDG-PET | positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose |
| 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 |
| 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 |
| IEC | independent ethics committees |
| IRB | institutional review board |
| IV | intravenous |
| IWRS | interactive web-response system |
| LD | longest diameter |
| LDH | lactate dehydrogenase |

| Abbreviation | Definition |
|---|---|
| LS | least square |
| M | mitosis phase of cell cycle |
| MATE1 or 2-K | multidrug and toxin extrusion 1 or 2-K |
| MDR1 | p-glycoprotein |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MRP1 or 2 | multidrug resistance protein 1 or 2 |
| NCI | National Cancer Institute |
| 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 |
| PD | progressive disease |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PK | pharmacokinetic |
| PP | per protocol |
| PR | partial response |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| Rb | retinoblastoma protein |
| RB-1 | retinoblastoma gene |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RH | relative humidity |
| [redacted] | [redacted] |
| RNASeq | RNA sequencing |
| S | synthesis phase of cell cycle in which DNA is replicated |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCLC | small cell lung cancer |
| SD | stable disease |
| SMC | safety monitoring committee |

| Abbreviation | Definition |
|---|---|
| SOP | standard operating procedure |
| $t_{1/2}$ | terminal half-life |
| $T_{max}$ | time to reach $C_{max}$ |
| TP53 | tumor protein 53 |
| 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 Previously Treated Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Topotecan Chemotherapy |
| Study Rationale | Chemotherapy-induced myelosuppression is a significant issue in cancer treatment, including treatment of SCLC. G1T28 (trilaciclib; 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.<br><br>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/pharmacodynamics 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 topotecan on Days 1 to 5 of 21-day cycles 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 topotecan and to evaluate the effect of G1T28 on chemotherapy-induced myelosuppression. |
| Clinical Phase | 1b/2a |
| Indication | Reduction of chemotherapy-induced myelosuppression |

Objectives

| | Part 1 (Phase 1b) | Parts 2A and 2B (Phase 2a) |
|---|---|---|
| **Primary Objectives** | | |
| Assess the DLTs and define the Phase 2 dose of G1T28 administered with topotecan | X | |
| Assess the safety and tolerability of G1T28 administered with topotecan | X | X |
| **Secondary Objectives** | | |
| Assess the PK profile of G1T28 | X | X[a] |
| Assess the PK profile of topotecan when administered with G1T28 | X | X[a] |
| Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of G1T28 administered with topotecan | X | X |
| Assess the incidence of febrile neutropenia | X | X |
| Assess the incidence of infections | X | X |
| Assess the utilization of RBC and platelet transfusions | X | X |
| Assess the utilization of hematopoietic growth factors | X | X |
| Assess the utilization of systemic antibiotics | X | X |
| Assess the incidence of chemotherapy dose reductions and dose interruptions overall | X | X |
| Assess the incidence of Grade 2 or greater nephrotoxicity | X | X |
| Assess tumor response based on RECIST, Version 1.1 | X | X |
| Assess PFS and overall survival | X | X |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

DLT = dose-limiting toxicity; PFS = progression-free survival;
PK = pharmacokinetic; QOL = quality of life; RBC = red blood cell;
RECIST = Response Evaluation Criteria in Solid Tumors;

a Limited population PK sampling in Parts 2A and 2B

| | |
|---|---|
| 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 topotecan for patients with previously treated extensive-stage SCLC. The study consists of 2 parts: a limited open-label, dose-finding portion (Part 1), and a randomized, double-blind, portion (Parts 2A and 2B). All parts 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.<br><br>**Part 1**<br><br>The goal of Part 1 is to assess the safety, including dose-limiting toxicities (DLTs), and PK of G1T28 administered at an initial 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) in combination with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle.<br><br>Six patients will initially be enrolled in Part 1. Depending on the evaluation of DLTs and PK parameters of G1T28 and topotecan 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 subjects treated with 200 mg/m$^2$, the target $AUC_{0\text{-}24\ 5h}$ is 3100 h•ng/mL. If the mean $AUC_{0\text{-}24\ 5h}$ of the cohort 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. 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 Part 1 prior to initiating Parts 2A and 2B of the study. If the G1T28 dose level for a subsequent cohort requires escalation, the increase will not exceed 30% from a previous dose level.<br><br>Since G1T28 has been shown to inhibit renal transporters for which topotecan is a substrate, there is a potential for increasing topotecan exposure when administered after G1T28. If topotecan exposure is significantly altered resulting in potential safety concerns, the safety monitoring committee (SMC) will evaluate the data and modify the dose of topotecan as appropriate. In particular, the SMC will closely evaluate the safety data if the mean topotecan CL in the first 6 patients is $\leq$ 0.14 L/min/m$^2$.<br><br>All dose escalation/de-escalation decisions will be based on Cycle 1 safety and PK data, which will be reviewed by a SMC composed of the sponsor, medical monitor, and the principal investigator(s) to determine the next dose level. If the G1T28 and/or topotecan 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 topotecan should have their G1T28 and/or topotecan dose adjusted accordingly, starting with their next scheduled cycle. Additional cohorts for Part 1 will be considered based on the review of safety and PK data by the SMC. The G1T28 and topotecan doses for Arm 1 of Parts 2A and 2B will be obtained by utilizing all available safety and PK data from patients enrolled in Part 1.

Each patient will be evaluated for toxicity during each cycle. The toxicity of G1T28 administered IV with topotecan 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 6 patients during Cycle 1 of Part 1, and the target PK parameters are achieved, then Part 1 will end and all subsequent patients will be enrolled into Parts 2A and 2B, utilizing a dose of G1T28 200 mg/m$^2$ in combination with topotecan. If an additional cohort(s) of 6 patients is enrolled in Part 1, then the dose for Parts 2A and 2B will be defined following evaluation of safety and PK data from the additional cohort(s) of patients.

Dose-limiting toxicities (applicable to Cycle 1 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; a delay of up to 1 week from the scheduled start of Cycle 2 is allowed for recovery of ANC and platelet count, and is not considered a DLT
- ≥ Grade 3 nonhematologic drug-related toxicity (nausea, vomiting, and diarrhea failing maximal medical management; fatigue lasting for > 72 hours)

Toxicities not clearly related to topotecan will also be considered for the purposes of determining DLTs.

**Part 2A**

In Part 2A, eligible patients will be randomized (2:1) to receive G1T28 or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle. In Arm 1, patients will receive the G1T28 (240 mg/m$^2$) + topotecan (0.75 mg/m$^2$) doses determined in Part 1 of the study, and in Arm 2, patients will receive placebo + topotecan 1.5 mg/m$^2$. There will be no intrapatient dose modifications of G1T28 in Part 2 of the study.

**Part 2B**

In order to accurately assess the impact of G1T28 on the safety and efficacy of topotecan, it is critical that topotecan exposures are similar in the topotecan + G1T28 and topotecan + placebo arms. Therefore, an additional arm of G1T28 240 mg/m$^2$ + topotecan 1.5 mg/m$^2$ will be investigated as Arm 1 in Part 2B of this study.

In Part 2B, eligible patients will be randomized (2:1) to receive G1T28 or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle. In Arm 1, patients will receive G1T28 (240 mg/mg$^2$) + topotecan (1.5 mg/m$^2$) and in Arm 2, patients will receive placebo + topotecan (1.5 mg/m$^2$).

**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, 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 $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline. A delay of 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 6.1.4, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). [redacted] 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 completion of the patient-reported outcome (PRO) scales, CBC assessment on Day 22, return for the Post-Treatment Visit, and complete the Survival Follow-up Phase of the study, which is to continue until at least 50% of the patients in Parts 2A and 2B 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 G1T28-03 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 commences at the time that informed consent is obtained and continues through the Post-Treatment Visit.

A SMC will review safety and PK of G1T28 and topotecan for all patients enrolled in Part 1 of the study. The committee will make recommendations for dose escalation/de-escalation based on the criteria listed in Sections 6.1.1.1 to 6.1.1.4.

An independent data monitoring committee (DMC) will monitor accumulating safety and patient disposition data approximately every 4 months during the Treatment Phase of Part 2A of the study, depending upon the enrollment rate. The independent DMC will also monitor accumulating safety and disposition data in Part 2B, with the first meeting occurring after approximately 10 patients have been enrolled, and then approximately every 4 months during the Treatment Phase, 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 (including brain metastases, if present at screening) 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. Brain scans with contrast (by CT or MRI) should be obtained with tumor assessment at screening. For those without brain metastases at screening, an additional scan should be performed at the Post-Treatment Visit for patients who have not progressed at the time of study drug discontinuation. For those with brain metastases, brain scans should be done with each tumor assessment. 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 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, within 4 weeks of study drug discontinuation and then 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, whichever occurs first. |
| Study Duration | The total study duration is at least 33 months.<br>Part 1 is expected to be approximately 17 months, assuming 12 months of accrual, 2 weeks for screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.<br>Part 2A will begin after the Phase 2 doses of G1T28 and topotecan (for Arm 1 of Part 2A) are identified from Part 1, which is expected to occur approximately 17 months after Part 1 begins (based on 12 months of accrual, 2 weeks of screening, 3 months of treatment, and time for the analysis of safety and PK data to identify the Phase 2 dose). Part 2A is expected to be approximately 16 months, assuming 11 months of accrual, 2 weeks of screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.<br>Part 2B will begin after enrollment in Part 2A is complete (ie, when approximately 45 patients are enrolled) and is expected to be approximately 14 months, assuming 9 months of accrual, 2 weeks of screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.<br>The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B have died. |
| Approximate Number of Patients | Up to 130 patients will be enrolled in the study. In Part 1, approximately 40 patients will be enrolled assuming 9 to 10 cohorts. In Part 2A, approximately 45 patients will be enrolled. In Part 2B, approximately 45 patients will be enrolled. |
| Number of Study Centers | Up to 60 centers in the 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.<br>1. Age $\geq$ 18 years<br>2. Unequivocally confirmed diagnosis of SCLC by histology or cytology, preferably including the presence of neuroendocrine features by immunohistochemistry<br>3. Progression during or after prior first- or second-line chemotherapy and eligible to receive topotecan therapy (immunotherapy treatment alone, ie, not administered with chemotherapy, should not be counted as a line of chemotherapy)<br>4. At least 1 target lesion that is measurable by RECIST, Version 1.1<br>5. Absolute neutrophil count $\geq 1.5 \times 10^9$/L<br>6. Platelet count $\geq 100 \times 10^9$/L |

| | |
|---|---|
| | 7. Creatinine ≤ 1.5 mg/dL and creatinine clearance (CrCl) of ≥ 60 mL/minute)<br>8. Total bilirubin ≤ 1.5 × upper limit of normal (ULN)<br>9. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases<br>10. Serum albumin ≥ 3 g/dL<br>11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2<br>12. All clinically significant toxicities from previous anticancer therapy must have resolved to ≤ Grade 1 (except for hemoglobin)<br>13. Contraception:<br>a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and negative serum or urine β-hCG test result at baseline. Females must be either postmenopausal, surgically sterile, or using an acceptable method of contraception in combination with a barrier method. 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 to be used in combination with a barrier method are an intrauterine device, contraceptive implant, oral contraceptive (stable dose of the same hormonal contraceptive product for at least 3 months prior to dosing), or a vasectomized partner. These methods are to be utilized during the study and for 3 months after discontinuation of treatment<br>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<br>14. Able to understand and sign an informed consent |
| Criteria for Exclusion | A patient will not be eligible for participation in this study if any of the following criteria apply. |

1. History of topotecan treatment for SCLC
2. Presence of 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. History of upper gastrointestinal bleeding, ulceration, perforation, or significant gastrointestinal disease within 12 months prior to study enrollment
10. Known human immunodeficiency virus (HIV) positive; known hepatitis B virus (HBV) positive; or known hepatitis C virus (HCV) positive that is symptomatic or requiring active therapy
11. 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)
12. Receipt of any systemic chemotherapy regimen within 4 weeks prior to enrollment or a noncytotoxic investigational medication within 2 weeks prior to enrollment
13. Receipt of any low-dose systemic chemotherapeutic agent given for a nononcologic purpose within 4 weeks prior to enrollment (eg, low-dose methotrexate for rheumatoid arthritis)
14. Hypersensitivity to any of the components of the formulation of topotecan
15. Legal incapacity or limited legal capacity
16. Pregnant or lactating women

| | |
|---|---|
| Chemotherapy Treatment | Part 1: Topotecan 1.5 mg/m$^2$ (initial dose level) administered as an IV infusion over 30 (±5) minutes daily on Days 1 to 5 of each 21-day cycle<br>Part 2: Topotecan dose level (0.75 mg/m$^2$) for Arm 1 of Part 2A is derived from Part 1 and topotecan 1.5 mg/m$^2$ will be the dose used for Arm 2 of Part 2A. Topotecan will be administered as described for Part 1.<br>Topotecan 1.5 mg/m$^2$ will be the dose used for Arms 1 and 2 of Part 2B. Topotecan will be administered as described for Part 1. |
| Test Articles Dosage and Administration | Part 1: G1T28 200 mg/m$^2$ (initial dose level) in 250 mL of dextrose 5% in water (D5W) or in sodium chloride solution 0.9% administered as an IV infusion over 30 (±5) minutes once daily on Days 1 to 5 of each 21-day cycle prior to the dose of chemotherapy<br>Parts 2A and 2B: G1T28 dose level (240 mg/m$^2$) is derived from Part 1 and G1T28 will be administered as described for Part 1 |
| Comparator Dosage and Administration | Placebo formulation of 250 mL of D5W or sodium chloride solution 0.9% administered as an IV infusion over 30 (±5) minutes once daily on Days 1 to 5 of each 21-day cycle prior to the dose 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 [redacted] |
| 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 Part 1 of the study, blood samples will be collected from all patients for the measurement of G1T28 and topotecan concentrations in plasma at the time points listed below.<br><br><u>Part 1: Cycle 1 Day 1</u><br>Blood samples will be collected at the following time points relative to the start of G1T28 infusion on Cycle 1 Day 1 for all patients enrolled in 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 topotecan), 1.5, 2, 2.5, 3, 4.5, 6.5, 8.5 (this time point may be optional if approved by the sponsor in advance), and 24.5 hours postdose (prior to G1T28 dose on Day 2). Blood samples collected at the following time points are relative to the start of G1T28: 1.5 to 24.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. The EOI sample for topotecan must be drawn after |

| | |
|---|---|
| | completing infusion of the drug and the actual times at which the samples were drawn should be documented.<br><br>Part 1: Cycle 1 Day 4<br>Blood samples will be collected at the following time points relative to the start of G1T28 infusion on Cycle 1 Day 4 for all patients enrolled in Part 1 of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (EOI of G1T28), 1 (EOI of topotecan), 1.5, 2, 2.5, 3, 4.5, 6.5, 8.5 (this time point may be optional if approved by the sponsor in advance), and 24.5 hours postdose (prior to G1T28 dose on Day 5). Blood samples collected at the following time points are relative to the start of G1T28: 1.5 to 24.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. The EOI sample for topotecan must be drawn after completing infusion of the drug and the actual times at which the samples were drawn should be documented.<br>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 and topotecan plasma concentration-time data.<br>Parts 2A and 2B: Cycle 1 Day 4<br>In addition, limited PK samples will be collected on Cycle 1 Day 4 in Parts 2A and 2B of the study for population PK analysis. Blood samples will be collected at the following time points relative to the start of G1T28 infusion on Cycle 1 Day 4 for all patients enrolled in Parts 2A and 2B of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (EOI of G1T28), 1 (EOI of topotecan), between 3 to 4 hours and between 5.5 to 6.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| Statistical Analysis | Data will be summarized descriptively by dose level, if applicable, and overall. Patients with the same dose level (Phase 2 dose level) in Parts 1, 2A, and 2B will be summarized together, unless described otherwise. In that case, patients with the same dose level will be summarized at the Phase 2 dose level together and separately by study part (Parts 1, 2A, and 2B). Treatment differences between treatment groups for Parts 2A and 2B will be calculated as G1T28 + topotecan therapy minus placebo + topotecan therapy. Select safety summaries will include combined data from Parts 1, 2A, and 2B. 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. All confidence intervals (CIs) will be 95%, unless stated otherwise.

A SMC will review safety and PK of G1T28 and topotecan for all patients enrolled in Part 1 of the study. The committee will make recommendations for dose escalation/de-escalation based on the criteria listed in Sections 6.1.1.1 to 6.1.1.4. A DMC will review accumulating safety and disposition data during the Treatment Phase for patients randomized in Parts 2A and 2B.

A final analysis for myelopreservation endpoints, and the first interim analysis for anti-tumor efficacy endpoints (including response rate, PFS and OS), will be performed after all patients have had the opportunity to receive at least 12 weeks (4 cycles) of treatment. The final anti-tumor analysis will coincide with the end of study analysis which will occur after at least 50% of patients have died. Additional anti-tumor analysis may be done with the timing to occur between the first interim anti-tumor analysis and the final anti-tumor analysis.

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 [redacted] endpoints. 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. 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 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.).

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. Treatment-emergent AEs will also be presented 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 the Kaplan-Meier method.<br><br>Blood samples will be collected in Part 1 of the study for the determination of G1T28 and topotecan plasma concentrations. Limited blood samples will also be collected in Parts 2A and 2B of the study for the determination of G1T28 plasma concentrations and population PK analysis. 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. PK 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. PK parameters will be calculated using noncompartmental methods based on the plasma concentration-time data. PK parameters will be summarized descriptively by visit and analyte. If applicable, G1T28 PK data will also be summarized by dose level. |
| Rationale for Number of Patients | Approximately 40 patients will be enrolled in Part 1 of the study (dose ranging), approximately 45 patients will be enrolled in Part 2A, and approximately 45 patients will be enrolled in Part 2B of the study. The Part 1 sample size is based on standard sample size for dose escalation to determine a tolerable G1T28 dose administered prior to topotecan on Days 1 to 5 of 21-day cycles. In Part 2 of the study, approximately 90 patients will be enrolled into 3 groups (G1T28 + topotecan 0.75 mg/m$^2$, G1T28 + topotecan 1.5 mg/m$^2$, and placebo + topotecan 1.5 mg/m$^2$). With 30 patients per group, the precision for point estimates in each group is as follows: the 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals are at most the observed proportion ± 0.167; and the 95% CI width for continuous endpoints using the t-distribution are the observed mean ± 0.373*standard deviation of the endpoint. Moreover, as there are approximately 130 patients for all data from Part 1, Part 2A, and Part 2B; the precision for point estimates is as follows: the 95% CI width for binary endpoints based on Wilson score intervals are at most the observed proportion ± 0.081; and the 95% CI width for continuous endpoints using the t-distribution are the observed mean ± 0.174*standard deviation of the endpoint. |

# 4. INTRODUCTION

## 4.1. Background

Chemotherapy-induced myelosuppression continues to represent the major dose-limiting toxicity (DLT) of cytotoxic chemotherapy, including topotecan used to treat extensive-stage small cell lung cancer (SCLC) after failure of first line (von Pawel 2014; Eckardt 2007). In Phase 3 clinical trials, topotecan 1.5 mg/m$^2$ resulted in significant myelosuppression (neutropenia 54% to 86%, leukopenia 75%, thrombocytopenia 43% to 54%, and anemia 30% to 31%), requiring frequent transfusions (50% to 53%) and growth factor use (von Pawel 2014; Eckardt 2007). 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 (trilaciclib; 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-independent 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 and Betticher 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

G1T28 has been evaluated in 1 completed Phase 1 study in healthy male and female volunteers (Study G1T28-1-01). Two Phase 1b/2a studies are currently ongoing in patients with SCLC: Study G1T28-02 and Study G1T28-03 (current study). A brief summary of the clinical data for all 3 studies is provided below and detailed information is presented in the G1T28 Investigator's Brochure (IB).

Please note that all data (except for Study G1T28-1-01) are from an open and active database and are subject to change.

### 4.2.1. Study G1T28-1-01

Study G1T28-1-01 was a Phase 1a, first-in-human, 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 intersubject 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 and PK/pharmacodynamic model simulations.

### 4.2.2. Study G1T28-02

This is an ongoing randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2a study of the safety and PK of G1T28 in combination with etoposide/carboplatin therapy for patients with newly diagnosed extensive-stage SCLC. The study consists of 2 parts: Part 1 is a limited open-label, dose-finding portion followed by an open-label, expansion portion at the selected dose to be used in Part 2. Part 2 is a randomized, double-blind, Phase 2a portion with 2 arms: etoposide (100 mg/m$^2$) on Days 1, 2, and 3 and carboplatin (AUC5) on Day 1 (EP) administered with G1T28 IV (240 mg/m$^2$) or placebo once daily on Days 1 to 3 of each 21-day cycle of E/P chemotherapy. 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.

As of 03 May 2017, Part 1 had completed enrollment, with 19 patients enrolled in Part 1: 10 in Cohort 1 (EP + G1T28 200 mg/m$^2$) and 9 in Cohort 2 (EP + G1T28 240 mg/m$^2$). All patients had discontinued study medication as follows: 13 due to treatment completion, 3 due to disease progression, 2 due to AEs considered unrelated to G1T28 (Grade 1 neutropenia unrelated to G1T28 and Grade 5 hypoxia unrelated to G1T28), and 1 decided to enter hospice. Nine patients had died, all due to their underlying SCLC. Three patients experienced DLTs that were used in combination with additional supporting data to select 240mg/m$^2$ G1T28 as the recommended Phase 2 dose to evaluate in Part 2. In Cohort 1, the DLTs were an asymptomatic Grade 2 neutropenia event leading to a delay in starting Cycle 2 and an asymptomatic Grade 4 thrombocytopenia event. In Cohort 2, the DLT was also an asymptomatic Grade 2 neutropenia event leading to a delay in starting Cycle 2. The most common (≥ 30%) treatment-emergent AEs (TEAEs) were neutropenia (63.2%), fatigue (57.9%), nausea (52.6%), constipation (47.4%), alopecia (42.1%), vomiting (42.1%), anemia (36.8%), and arthralgia (31.6%). The most common (≥ 15%) G1T28-related TEAEs were nausea (21.1%), vomiting (21.1%), fatigue (21.1%), and diarrhea (15.8%). There was 1 G1T28-related ≥ Grade 3AE (creatinine increased) and no G1T28-related SAEs.

As of 15 June 2017, Part 2 had completed enrollment, with a total of 77 patients but the data remains blinded. Of the 77 patients who were evaluable for safety as of the data cutoff date, 23 had discontinued study medication as follows: 9 due to treatment completion, 7 due to disease progression, 3 due to AEs (Grade 2 infusion reaction unlikely related to G1T28, Grade 2 platelet count decreased unlikely related to G1T28, and Grade 5 respiratory failure unrelated to G1T28), 2 due to other (Grade 5 respiratory failure unlikely related to G1T28 and therapy withheld for > 2 weeks), 1 due to withdrawal of consent, and 1 withdrawal by the investigator. Four of the 77 patients have died; 3 due to their underlying SCLC and 1 due to Grade 5 respiratory failure considered unrelated to any study medications. The most common (≥ 20%) TEAEs were neutropenia (41.1%), fatigue (26.0%), anemia (24.7%), nausea (24.7%), and thrombocytopenia (23.3%). Please note that these data are confounded by the fact that unblinding has not occurred and that approximately 50% of these patients did not receive G1T28.

### 4.2.3. Study G1T28-03 (Current Study)

In the current study (G1T28-03), as of 15 June 2017, Part 1 has completed enrollment, with 32 patients enrolled in 7 cohorts (Table 4-1); while Part 2 is ongoing and remains blinded, with 17 patients in total enrolled. In the previous protocol Version 4 (Amendment 3), Part 2 (designated Part 2A in the present protocol Version 5 [Amendment 4]) had 2 arms: topotecan (0.75 mg/m$^2$) IV once daily administered with G1T28 (240 mg/m$^2$) IV once daily on Days 1 to 5 versus topotecan (1.5 mg/m$^2$) IV once daily administered with placebo once daily on Days 1 to 5.

**Table 4-1 G1T28-03: Summary of Dose-Limiting Toxicities in Part 1 of the Study**

| | Cohort | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| Topotecan Dose ($mg/m^2$) | 1.5 | 1.25 | 0.75 | 0.75 | 0.75 | 0.75 | 1.0 |
| G1T28 Dose ($mg/m^2$) | 200 | 200 | 200 | 240 | 280 | 240 | 240 |
| Subjects Enrolled (N) | 2 | 3 | 4 | 5 | 7 | 3 | 8[a] |
| DLTs (n) | 2 (100%) | 2 (67%) | 2 (50%) | 0 | 3 (43%) | 0 | 2 (33%) |
| ANC < $0.5 \times 10^9$/L lasting for > 7 days | 2 (100%) | 2 (67%) | 2 (50%) | 0 | 0 | 0 | 1 (14%) |
| Grade 4 thrombocytopenia or > Grade 3 thrombocytopenia with bleeding | 1 (50%) | 1 (33%) | 0 | 0 | 2 (29%) | 0 | 1 (14%) |
| Unable to start next cycle of chemotherapy due to lack of recovery to an ANC > $1.5 \times 10^9$/L and platelet count > $100 \times 10^9$/L within 1 week of the planned start date (ie, > 1 week delay) | 0 | 0 | 0 | 0 | 1 (14%) | 0 | 0 |

a Eight patients were enrolled, but only 6 were evaluable for DLTs. One patient discontinued study drug after Day 1 due to a peripheral IV site reaction (subject withdrew to receive topotecan off study) and did not complete the chemotherapy cycle and 1 patient was incorrectly dosed with 200 $mg/m^2$ G1T28.

Of the 32 patients enrolled in Part 1, 30 have discontinued study medication as follows: 25 due to disease progression, 3 due to withdrawal of consent, and 2 due to AEs (Grade 2 myocardial infarction unlikely related to G1T28 and Grade 2 fatigue unrelated to G1T28). Twenty of the 32 patients have died, with 18 deaths due to the underlying SCLC, 1 death due to respiratory failure and encephalopathy, and 1 death for which the cause of death was unknown. Of the 32 patients enrolled in Part 1, 30 were evaluable for DLTs and 11 (37%) experienced a DLT as described above in Table 4-1; no DLTs were observed in Cohort 6, in which patients received the dose determined to be taken forward in Part 2. The most common (≥ 30%) TEAEs were neutropenia (71.9%), anemia (68.8%), thrombocytopenia (68.8%), fatigue (53.1%), nausea (40.6%), constipation (34.4%), dyspnea (34.4%), and white blood cell decreased (31.1%). The only G1T28-related TEAE that occurred with a frequency ≥ 10% was headache. There were no G1T28-related SAEs and 3 patients with G1T28-related ≥ Grade 3/4 AEs (anemia, thrombocytopenia, and neutropenia).

Of the 17 patients enrolled in Part 2 (designated Part 2A in the current protocol Amendment 4), 6 have discontinued study medication as follows: 3 due to disease progression, 2 due to withdrawal of consent, and 1 due to an AE (Grade 4 pancytopenia considered unrelated to G1T28). Two patients have died, both due to their underlying SCLC. The most common (≥ 15%) TEAEs were thrombocytopenia (41.2%), neutropenia (35.3%), anemia (29.4%), fatigue (29.4%), nausea (29.4%), diarrhea (23.5%), vomiting (23.5%), dehydration (23.5%), hyponatremia (17.6%), and febrile neutropenia (17.6%). Please note that these data are confounded by the fact that unblinding has not occurred and that approximately 33% of these patients did not receive G1T28.

## 4.3. [redacted]

[redacted]

### 4.3.1. Pharmacology Studies

Through a structure-based design approach to optimize potency, selectivity, and drug metabolism and PK properties, G1 Therapeutics, Inc. identified 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 complete blood count (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 and Betticher 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. [redacted]

[redacted]

Topotecan is primarily excreted in the urine as unchanged drug as its primary route of elimination (accounting for approximately 50% of elimination [Herben 1996]). Recent in vitro analysis has shown that topotecan is a substrate of MATE1 and MATE2, with an apparent Km of 70 μM and 60 μM, respectively (Tanihara 2007). Since G1T28 has been shown to inhibit these 2 renal transporters in vitro, there is a potential for increasing topotecan exposure. However, the relative contribution of MATE1 and MATE2 in topotecan clearance has not been established. In the present Study G1T28-03, IV G1T28 will be administered prior to IV topotecan on Days 1 to 5 of 21-day cycles in patients with adequate renal function. In Part 1 of the study, PK of G1T28 and topotecan will be assessed on Days 1 and 4 of the first cycle. In addition, frequent CBCs will be assessed. Since myelotoxicity is the major toxicity of topotecan, this will be monitored closely in this study. If PK or safety data suggest that topotecan exposure is significantly altered resulting in potential safety concerns, the SMC (see Section 6.1.1.4) will evaluate the data and suggest dose modifications to either G1T28 and/or topotecan, as appropriate.

**4.3.3.** [redacted]

[redacted]

**4.3.4.** [redacted]

[redacted]

- [redacted]
- Effects on liver: Daily IV doses of G1T28 in rats at ≥ 10 mg/kg/day (≥ 60 mg/m$^2$/day) [redacted]

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 topotecan, which presents a genotoxic hazard to human subjects. In this context, any slight additional genotoxic hazard posed by G1T28 is negligible.

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 and Betticher 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/pharmacodynamic parameters from the Phase 1a study and a preclinical PK/pharmacodynamic 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 topotecan on Days 1 to 5 of 21-day cycles 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 topotecan and to evaluate the effect of G1T28 on chemotherapy-induced myelosuppression.

### 4.4.1. Selection of G1T28 and Topotecan Doses for Part 2A

Pharmacokinetic assessments across Study G1T28-02 and G1T28-03 revealed that the PK parameters for G1T28 at 200 mg/m$^2$ were similar in each study. Additionally, it was observed that the exposure (AUC) of 200 mg/m$^2$ G1T28 was slightly lower than expected in patients based on the extrapolated AUC (3100 h*ng/mL) seen in the previous healthy volunteer study at 192 mg/m$^2$ (Study G1T28-1-01). Based on these observations and relevant safety data, the SMC (Section 6.1.1.5) from both studies independently decided to increase the dose of G1T28 to 240 mg/m$^2$, and the G1T28-03 SMC subsequently recommended testing 280 mg/m$^2$. In Study G1T28-03, the 240 mg/m$^2$ dose achieved the target AUC of 3100 h*ng/mL (3180 and 3120 h*ng/mL, on Days 1 and 4, respectively). However, exposures following administration of 280 mg/m$^2$ were significantly higher and resulted in accumulation (3570 and 4750 h*ng/mL on Days 1 and Day 4, respectively), which had not been observed at lower dose levels. Due to the level of accumulation and accompanying safety data, the 280 mg/m$^2$ dose was not recommended by the G1T28-03 SMC as the Phase 2a dose.

Evaluation of DLTs in both studies (Section 4.2.2 and 4.2.3) supported the selection of G1T28 240 mg/m$^2$ as the Phase 2a dose. In Study G1T28-02, two DLTs were observed with G1T28 200 mg/m$^2$, whereas only 1 DLT was observed with G1T28 240 mg/m$^2$. Review of hematology data presented by cohort and by G1T28 dose level also supported the selection of 240 mg/m$^2$ as the recommended Phase 2a dose.

Determination of the recommended Phase 2a dose for G1T28 administered prior to topotecan (Arm 1 of Part 2A in the current protocol Amendment 4) was complicated by a presumed DDI, which resulted in an apparent reduced topotecan CL and increased topotecan exposure (as discussed in Section 4.4.2) compared to historical controls (Saltz 1993; Van Warmerdam 1995; O'Reilly 1996; Gallo 2000; Montazeri 2002; Mould 2002). Based on available safety, PK, and preliminary response data, the SMC considered 2 potential dose regimens for the Phase 2a portion (designated Arm 1 of Part 2A in current protocol Amendment 4) of the

present Study G1T28-03 (G1T28 240 mg/m$^2$ + topotecan 0.75 mg/m$^2$, Cohorts 4/6, or G1T28 240 mg/m$^2$ + topotecan 1.0 mg/m$^2$, Cohort 7). Pharmacokinetic data demonstrated that the mean 5-day AUC of topotecan 0.75 mg/m$^2$ dosed with G1T28 240 mg/m$^2$ (Cohorts 4 and 6) was within the expected range of the 5-day AUC of topotecan 1.5 mg/m$^2$ monotherapy compared to historical controls, whereas the mean 5-day AUC of topotecan 1 mg/m$^2$ dosed with G1T28 240 mg/m$^2$ (Cohort 7) was at the upper end of the historical range and for a few patients was higher than the upper end of the historical control range. In addition, as outlined above in Section 4.2.3, 2 of 6 evaluable patients (33%) in Cohort 7 experienced DLTs, whereas no patients in Cohorts 4 and 6 (of 8 evaluable patients) experienced a DLT.

### 4.4.2. Selection of G1T28 and Topotecan Dose for Part 2B

At the first G1T28-03 DMC meeting for Part 2 (held in June 2017; Section 6.1.2), available topotecan PK data collected from patients enrolled thus far in Arms 1 and 2 of Part 2A (per the current protocol Amendment 4) were reviewed by the unblinded clinical pharmacokineticist. It was noted that the topotecan PK parameters observed for the 12 patients enrolled in Arm 1 (G1T28 240 mg/m$^2$ + topotecan 0.75 mg/m$^2$) were similar to the data obtained in Part 1 of the study for patients receiving the same doses of G1T28 and topotecan (Table 4-2). However, the topotecan PK parameters for the 6 patients enrolled in Arm 2 (placebo + topotecan 1.5 mg/m$^2$) were inconsistent with the historical controls from published literature. Two more contemporary topotecan PK studies, that were not included in the original historical controls from published literature, reported similar topotecan CL values to those of patients in Arm 2 of Part 2A, with mean CL values of 0.157 and 0.121 L/min/m$^2$ (Stewart 2014; Molina 2008).

In order to accurately assess the impact of G1T28 on the safety and efficacy of topotecan, it is critical that topotecan exposures are similar in the topotecan + G1T28 and topotecan + placebo arms. Therefore, an additional arm of G1T28 240 mg/m$^2$ + topotecan 1.5 mg/m$^2$ will be investigated as Arm 1 in Part 2B of this study. As described in the rationale presented in Section 4.4.1, the dose of G1T28 will remain at 240 mg/m$^2$ for Arm 1 of Part 2B.

**Table 4-2 G1T28-03: Comparison of Topotecan Pharmacokinetic Parameters**

| | N | CL (L/min/m$^2$) | 5-Day AUC (min*nM) |
|---|---|---|---|
| Historical literature 1993-2002[a] | | 0.34 (0.19 to 0.57) | 48,127 (28,735 to 84,866) |
| Historical literature 2008-2014 | | 0.14[b,c] (0.11 to 0.17) | 60,144[b] (22,996 to 93,033) |
| Topotecan 0.75 mg/m$^2$ (with G1T28; G1T28-03 Part 1) | 19 | 0.17 (0.080 to 0.41) | 54,900 (20,000 to 102,000) |
| Topotecan 0.75 mg/m$^2$ (Arm 1 with G1T28; Study G1T28-03 Part 2A) | 12 | 0.17 (0.12-0.33) | 50,800 (24,600 to 70,500) |
| Topotecan 1.5 mg/m$^2$ (Arm 2 with placebo; Study G1T28-03 Part 2A) | 6 | 0.13 (0.09 to 0.18) | 133,000 (91,100 to 180,000) |

a Historical mean clearance values from 6 published reports were used to generate a range of AUC × 5 values (Saltz 1993; Van Warmerdam 1995; O'Reilly 1996; Gallo 2000; Montazeri 2002; Mould 2002).

b Stewart 2014

c Molina 2008

Available safety data from Arms 1 and 2 of Part 2A (current protocol Amendment 4) were also reviewed at the G1T28-03 DMC meeting. The DMC did not note any safety concerns in either arm and recommended to continue the study without modification. Topotecan is highly myelosuppressive, and preliminary data suggests that G1T28 does not appear to add to the myelotoxicity of topotecan, consistent with the underlying hypothesis that transient CDK4/6 inhibition in combination with cytotoxic chemotherapy can provide myeloprotection. Data observed in Study G1T28-02 (G1T28 in combination with EP [first-line therapy for SCLC]) also support this hypothesis.

Therefore, it is reasonable to test an additional arm of G1T28 240 mg/m$^2$ + topotecan 1.5 mg/m$^2$ in Part 2B of this study. However, since there are currently no available data for this combination, the DMC will review safety data after approximately 10 patients have been enrolled in Part 2B. The frequency of additional meetings will be determined following review of the safety findings from the first meeting, and on the anticipated enrollment rate; at a minimum, the DMC will meet approximately every 4 months.

## 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 5 of every 21-day cycle of topotecan therapy in the present

study. In conclusion, the potential benefits of combining G1T28 at a dose of 200 mg/m$^2$ with topotecan to protect the bone marrow HSPCs outweigh the potential risks.

# 5. STUDY OBJECTIVES

The primary, secondary, [redacted] objectives of this study are presented in Table 5-1.

**Table 5-1 G1T28-03: Study Objectives**

| | Part 1 (Phase 1b) | Parts 2A and 2B (Phase 2a) |
|---|---|---|
| **Primary Objectives** | | |
| Assess the DLTs and define the Phase 2 dose of G1T28 administered with topotecan | X | |
| Assess the safety and tolerability of G1T28 administered with topotecan | X | X |
| **Secondary Objectives** | | |
| Assess the PK profile of G1T28 | X | X[a] |
| Assess the PK profile of topotecan when administered with G1T28 | X | X[a] |
| Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of G1T28 administered with topotecan | X | X |
| Assess the incidence of febrile neutropenia | X | X |
| Assess the incidence of infections | X | X |
| Assess the utilization of RBC and platelet transfusions | X | X |
| Assess the utilization of hematopoietic growth factors | X | X |
| Assess the utilization of systemic antibiotics | X | X |
| Assess the incidence of chemotherapy dose reductions and dose interruptions overall | X | X |
| Assess the incidence of Grade 2 or greater nephrotoxicity | X | X |
| Assess tumor response based on RECIST, Version 1.1 | X | X |
| Assess PFS and overall survival | X | X |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

DLT = dose-limiting toxicity; PFS = progression-free survival; PK = pharmacokinetic; [redacted] RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

a Limited population PK sampling in Parts 2A and 2B

# 6. INVESTIGATIONAL PLAN

## 6.1. Overall Study Design and Plan

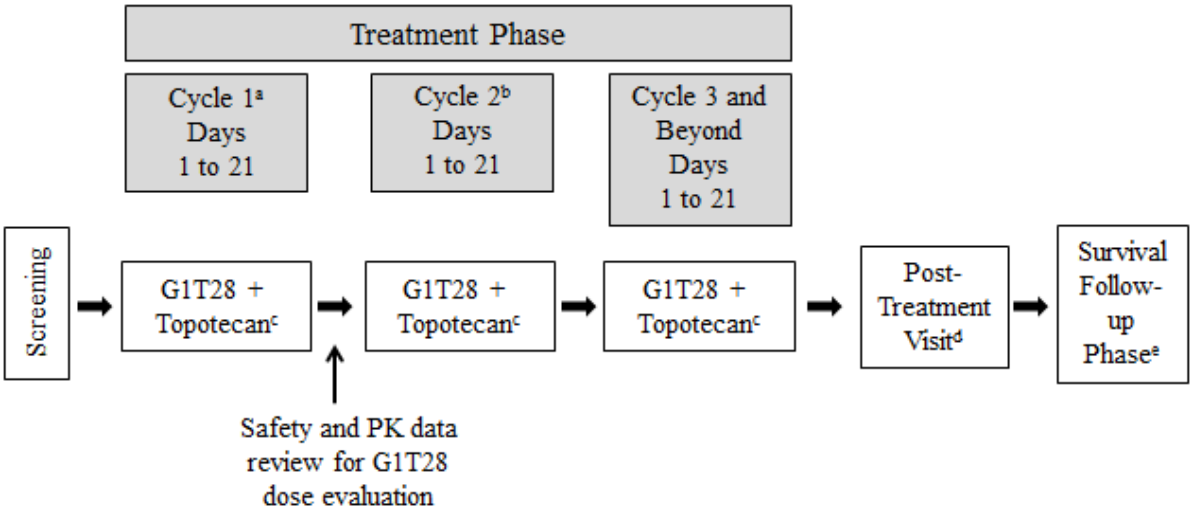
This is a randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2a study of the safety and PK of G1T28 in combination with topotecan for patients with previously treated extensive-stage SCLC. The study consists of 2 parts: a limited open-label, dose-finding portion (Part 1), and a randomized, double-blind, placebo-controlled portion (Parts 2A and 2B). All parts 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. [redacted]

### 6.1.1. Part 1

The goal 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 an initial dose of 200 mg/m$^2$ once daily in combination with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 6-1).

**Figure 6-1 Study Schema: Part 1**




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

b G1T28 + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. 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 topotecan on Days 1 to 5 of 21-day cycles

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

e The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B of the study have died.

#### 6.1.1.1. Definition of Dose-Limiting Toxicities (Applicable to Cycle 1 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; a delay of up to 1 week from the scheduled start of Cycle 2 is allowed for recovery of ANC and platelet count, and is not considered a DLT
- $\geq$ Grade 3 nonhematologic toxicity (nausea, vomiting, and diarrhea failing maximal medical management; fatigue lasting for > 72 hours)

Toxicities not clearly related to topotecan 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, the present study 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 6 patients in 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. The adjusted dose, if necessary, will be tested in 6 additional patients enrolled in Part 1 prior to initiating Parts 2A and 2B of the study. 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. The same criteria for the mean PK parameters ($AUC_{0\text{-}24.5h}$) should be used for modifying the G1T28 dose (if required) for patients enrolled in additional cohort(s) in Part 1.

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

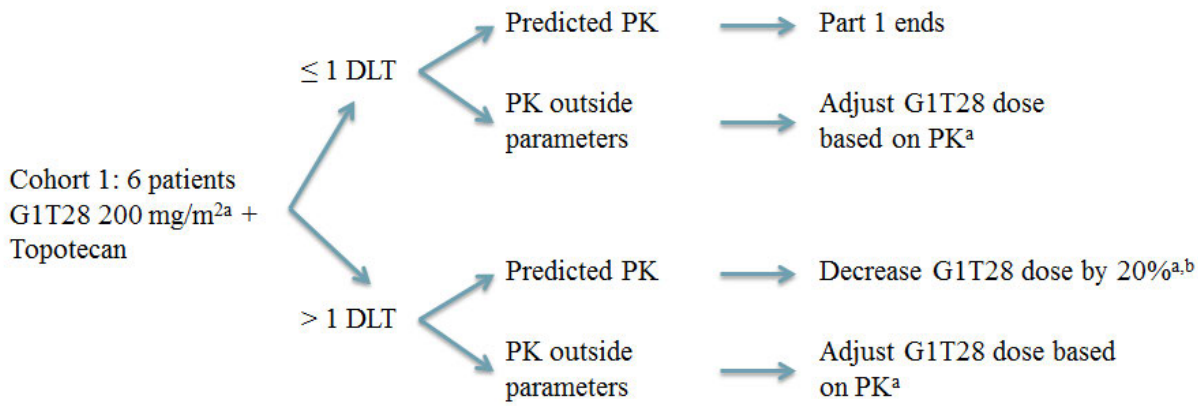
Six patients will initially be enrolled in Part 1 and will receive an initial dose of G1T28 200 mg/m$^2$ in combination with standard topotecan therapy (see Section 8.1). Safety and PK parameters from this initial cohort of 6 patients during Cycle 1 will be considered in making dose escalation/de-escalation 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 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.

- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of Part 1 and the G1T28 PK parameters are as predicted (Section 6.1.1.2), Part 1 will end and all subsequent patients will be enrolled into Parts 2A and 2B, utilizing a dose of G1T28 of 200 mg/m$^2$ in combination with topotecan.
- If there is ≤ 1 DLT in the first cohort of 6 patients during Cycle 1 of Part 1, and the 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 topotecan. For assessment of data from the second cohort enrolled in 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 Part 1 and the 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/pharmacodynamic 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 topotecan. For assessment of data from the second cohort enrolled in 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 Part 1 and the 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 topotecan. For assessment of data from the second cohort enrolled in 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 topotecan and the PK parameters from these 6 patients 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 topotecan. For assessment of data from the third cohort enrolled in Part 1, please see the decision tree in Figure 6-2.
- If there is > 1 DLT following the second dose reduction of G1T28 and the PK parameters from these 6 patients 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 pending SMC review and recommendations for either continued enrollment or permanent closure of the cohort

**Figure 6-2 G1T28 Dose Evaluation**




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

b Maximum of 2 G1T28 dose reductions are allowed (first dose reduction to 160 mg/m$^2$ and second dose reduction to 130 mg/m$^2$)

All dose-escalation/de-escalation decisions will be based on Cycle 1 safety and available PK data and will be reviewed by a safety monitoring committee (SMC) composed of the sponsor, medical monitor, and the principal investigator(s) to determine the next dose level. If the G1T28 and/or topotecan 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 topotecan should have their G1T28 and/or topotecan dose adjusted accordingly, starting with their next scheduled cycle. Additional cohorts for Part 1 will be considered based on review of the safety and PK data by the safety monitoring committee. The doses of G1T28 and topotecan for Arm 1 of Parts 2A and 2B will be obtained by utilizing all available safety and

PK data from patients enrolled in Part 1. There will be no intrapatient dose modifications of G1T28 in Parts 2A and 2B of the study.

Each patient will be evaluated for toxicity during each cycle. The toxicity of IV G1T28 administered with topotecan 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. Topotecan Dose Evaluation

Since G1T28 has been shown to inhibit renal transporters for which topotecan is a substrate, there is a potential for increasing topotecan exposure when administered after G1T28 (see Section 4.3.2). However, the relative contribution of these transporters in topotecan clearance has not been established. Therefore, in Part 1 of the present Study G1T28-03, PK of G1T28 and topotecan will be assessed on Days 1 and 4 of the first cycle.

Previous studies of the most frequently used topotecan schedule (ie, 30-minute IV infusion on Days 1 to 5 every 21 days) have shown that total topotecan AUC (ie, from Day 1 to Day 5) of higher than 75,000 nM·min was associated with a high probability of major toxicity (myelosuppression), whereas patients with a total AUC of lower than 37,500 nM·min had a limited decrease in neutrophil count (Grochow 1992; O'Reilly 1996a; O'Reilly 1996b; Gerrits 1998; Montazeri 2002). In the guidelines provided by the manufacturer, dose adjustments for renal clearance are suggested for moderate renal impairment (creatinine clearance [CrCl] 20 to 39 mL/min). Patients with moderate renal impairment have been shown to have a topotecan clearance of 0.14 L/min/$m^2$ compared to 0.4 L/min/$m^2$ in patients with normal renal function (CrCl ≥ 60 mL/min, which is required for inclusion in the study; Section 7.1.1).

Since myelosuppression is the major toxicity of topotecan and G1T28 is being developed to reduce myelosuppression following cytotoxic chemotherapy, CBC monitoring will be followed closely in this study. If topotecan exposure is significantly altered resulting in potential safety concerns, the SMC will evaluate the data and modify the dose of topotecan as appropriate. In particular, the SMC will closely evaluate the safety data if the mean topotecan CL in the first 6 patients is ≤ 0.14 L/min/$m^2$.

#### 6.1.1.5. Safety Monitoring Committee

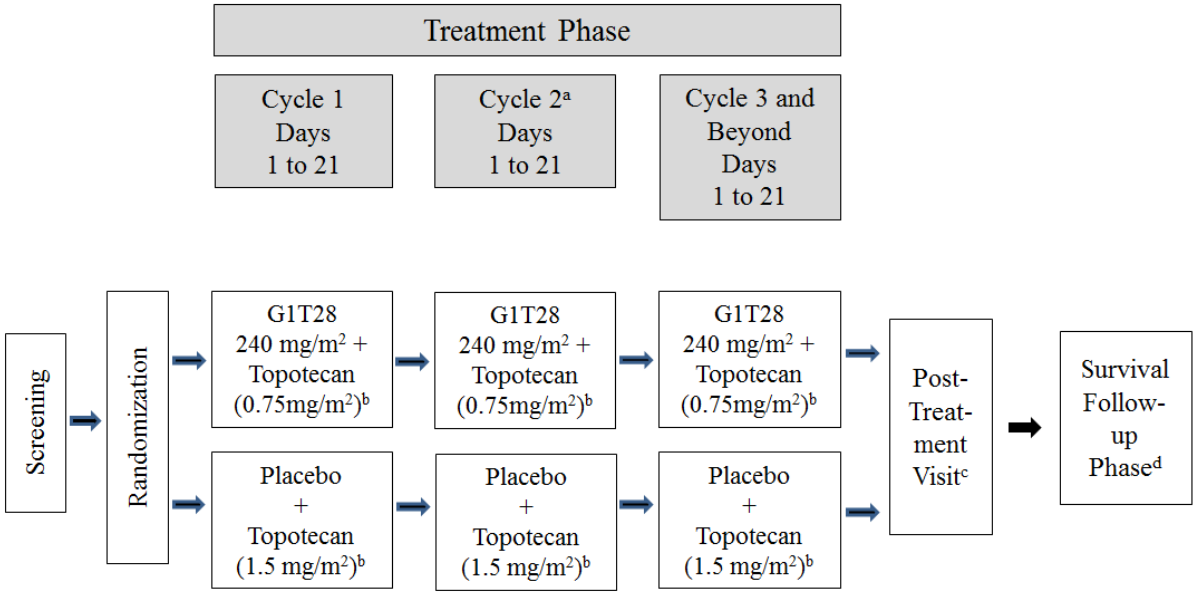
The SMC will be set up to review safety of G1T28 for all patients enrolled in Part 1 of the study. The SMC will consist of the principal investigator(s), the medical monitor, and G1 Therapeutics representatives and/or designees. The SMC will review any DLTs, SAEs, PK, and all other available data. The committee will make recommendations for dose escalation/de-escalation of G1T28 and/or topotecan based on the criteria listed in Sections 6.1.1.1 to 6.1.1.4. While the dose evaluation criteria will be used to guide all dose decisions, the SMC will be responsible for all G1T28 and/or topotecan dose and cohort recommendations, including any adjustments to the PK collection schedule. If the G1T28 and/or topotecan 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 topotecan should have their G1T28 and/or topotecan dose adjusted accordingly, starting with their next scheduled cycle.

### 6.1.2. Part 2A

In Part 2A, eligible patients will be randomized (2:1) to receive G1T28 or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 6-3). In Arm 1, patients will receive the G1T28 (240 mg/m$^2$) + topotecan (0.75 mg/m$^2$) doses originally determined in Part 1 of the study, and in Arm 2, patients will receive placebo + topotecan 1.5 mg/m$^2$.

Randomization will be stratified on the basis of Eastern Cooperative Oncology group (ECOG) performance status (0 to 1 versus 2) and sensitivity to first-line treatment (sensitive: complete response [CR], partial response [PR], or stable disease [SD] after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: progressive disease [PD] as best response to first-line therapy or progression-free interval < 90 days after completion of first line therapy). There will be no intrapatient dose modifications of G1T28 in Parts 2A of the study.

**Figure 6-3 Study Schema: Part 2A**




a G1T28 or placebo + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. 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 or placebo will be administered prior to the administration of topotecan on Days 1 to 5 of 21-day cycles

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

d The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B of the study have died.

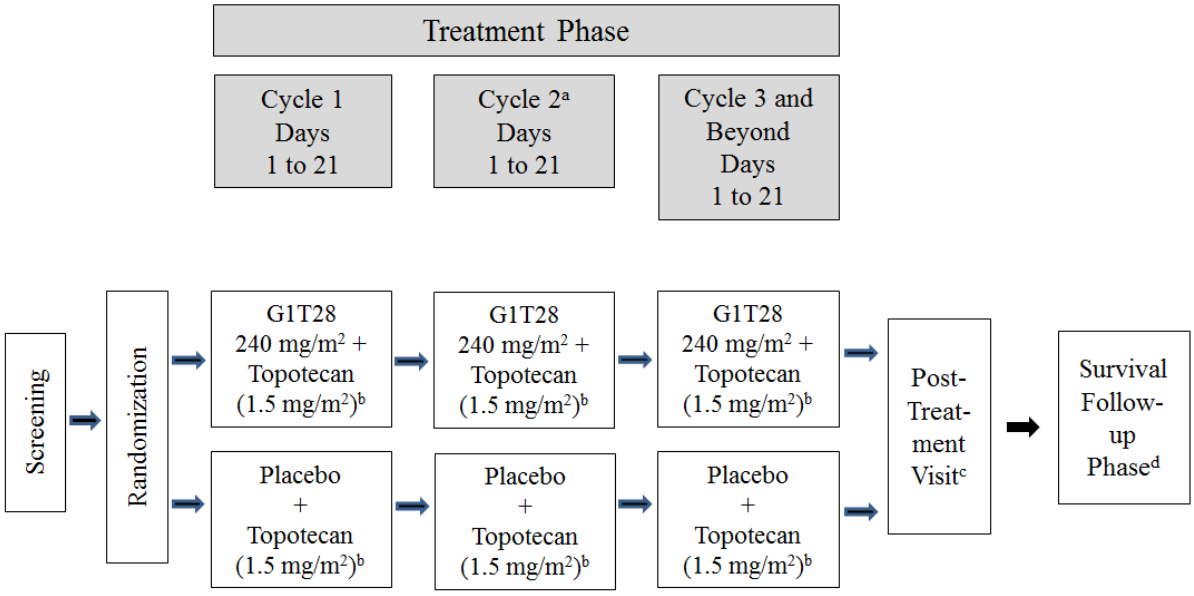
An independent data monitoring committee (DMC) will monitor accumulating safety and disposition data approximately every 4 months during the Treatment Phase of Part 2A of the study, depending upon the enrollment rate. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

### 6.1.3. Part 2B

In Part 2B, eligible patients will be randomized (2:1) to receive G1T28 or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 6-4). In Arm 1, patients will receive G1T28 (240 mg/mg$^2$) + topotecan (1.5 mg/m$^2$) and in Arm 2, patients will receive placebo + topotecan (1.5 mg/m$^2$).

As described above in Section 6.1.2 for Part 2A, randomization for Part 2B will also be stratified on the basis of ECOG performance status (0 to 1 versus 2) and sensitivity to first-line treatment (sensitive: CR, PR, or SD after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: PD as best response to first-line therapy or progression-free interval < 90 days after completion of first-line therapy). There will be no intrapatient dose modifications of G1T28 in Part 2B of the study.

**Figure 6-4 Study Schema: Part 2B**




a G1T28 or placebo + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. 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 or placebo will be administered prior to the administration of topotecan on Days 1 to 5 of 21-day cycles

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

d The Survival Follow-up Phase will continue until at least 50% of the patients in Parts 2A and 2B of the study have died.

An independent DMC will monitor accumulating safety and patient disposition data in Part 2B, with the first meeting occurring after approximately 10 patients have been enrolled, and then approximately every 4 months during the Treatment Phase, depending upon the enrollment rate. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

### 6.1.4. 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, 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 $\leq$ 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.). [redacted] 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 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 completion of 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 G1T28-03 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 33 months.

Part 1 is expected to be approximately 17 months, assuming 12 months of accrual, 2 weeks for screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.

Part 2A will begin after the Phase 2 doses of G1T28 and topotecan (for Arm 1 of Part 2A) are identified from Part 1, which is expected to occur approximately 17 months after Part 1 begins (based on 12 months of accrual, 2 weeks of screening, 3 months of treatment, and time for the analysis of safety and PK data to identify the Phase 2 dose). Part 2A is expected to be approximately 16 months, assuming 11 months of accrual, 2 weeks of screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.

Part 2B will begin after enrollment in Part 2A is complete (ie, when approximately 45 patients are enrolled) and is expected to be approximately 14 months, assuming 9 months

of accrual, 2 weeks of screening, 3 months of treatment (assuming 4 cycles), and 1 month of safety follow-up.

The Survival Follow-up Phase of the study will continue until at least 50% of the patients in Parts 2A and 2B have died.

### 6.1.5. Safety Assessments

Safety assessments 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 6.1.6), progression-free survival (PFS), and overall survival 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.

### 6.1.6. Tumor Assessment

For tumor assessment, all sites of disease (including brain metastases, if present at screening) 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. Brain scans with contrast (by CT or MRI) should be obtained with tumor assessment at screening. For those without brain metastases at screening, an additional scan should be performed at the Post-Treatment Visit for patients who have not progressed at the time of study drug discontinuation. For those with brain metastases, brain scans should be done with each tumor assessment. 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 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, within 4 weeks of study drug discontinuation and then 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 130 patients will be enrolled in the study.

In Part 1, approximately 40 patients will be enrolled assuming 9-10 cohorts.

In Part 2A, approximately 45 patients will be enrolled.

In Part 2B, approximately 45 patients will be enrolled.

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

### 7.1.1. Inclusion Criteria

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

1. Age ≥ 18 years
2. Unequivocally confirmed diagnosis of SCLC by histology or cytology, preferably including the presence of neuroendocrine features by immunohistochemistry
3. Progression during or after prior first- or second-line chemotherapy and eligible to receive topotecan therapy (immunotherapy treatment alone, ie, not administered with chemotherapy, should not be counted as a line of chemotherapy)
4. At least 1 target lesion that is measurable by RECIST, Version 1.1 (Eisenhauer 2009)
5. Absolute neutrophil count ≥ $1.5 \times 10^9$/L
6. Platelet count ≥ $100 \times 10^9$/L
7. Creatinine ≤ 1.5 mg/dL and CrCl of ≥ 60 mL/min
8. Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
9. AST and ALT ≤ 2.5 × ULN; ≤ 5 × ULN in the presence of liver metastases
10. Serum albumin ≥ 3 g/dL
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
12. All clinically significant toxicities from previous anticancer therapy must have resolved to ≤ Grade 1 (except for hemoglobin)

13. Contraception:

    a. For females: All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and negative serum or urine β-hCG test result at baseline. Females must be either postmenopausal, surgically sterile, or using an acceptable method of contraception in combination with a barrier method. 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 to be used in combination with a barrier method are an intrauterine device, contraceptive implant, oral contraceptive (stable dose of the same hormonal contraceptive product for at least 3 months prior to dosing), or a vasectomized partner. These methods are to be utilized 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.

14. Able to understand and sign an informed consent

### 7.1.2. Exclusion Criteria

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

1. History of topotecan treatment for SCLC

2. Presence of 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. History of upper gastrointestinal bleeding, ulceration, perforation, or significant gastrointestinal disease within 12 months prior to study enrollment

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

11. 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)

12. Receipt of any systemic chemotherapy regimen within 4 weeks prior to enrollment or a noncytotoxic investigational medication within 2 weeks prior to enrollment

13. Receipt of any low-dose systemic chemotherapeutic agent given for a nononcologic purpose within 4 weeks prior to enrollment (eg, low-dose methotrexate for rheumatoid arthritis)

14. Hypersensitivity to any of the components of the formulation of topotecan

15. Legal incapacity or limited legal capacity

16. 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 in combination with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle. All dose escalation/de-escalation decisions and additional cohorts of patients to be enrolled in Part 1, if any, will be based on Cycle 1 safety and PK data (see Section 6.1.1). If the G1T28 and/or topotecan 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 topotecan should have their G1T28 and/or topotecan dose adjusted accordingly, starting with their next scheduled cycle.

Patients enrolled in Arm 1 of Part 2A will receive the dose of G1T28 derived from Part 1 administered IV once daily (240 mg/m$^2$) in combination with the dose of topotecan derived from Part 1 (0.75 mg/m$^2$) on Days 1 to 5 of each 21-day chemotherapy cycle. Patients enrolled in Arm 1 of Part 2B will receive G1T28 IV once daily (240 mg/m$^2$) in combination with topotecan (1.5 mg/m$^2$) on Days 1 to 5 of each 21-day chemotherapy cycle. Patients enrolled in Arm 2 of both Parts 2A and 2B will receive placebo administered IV once daily in combination with topotecan 1.5 mg/m$^2$ on Days 1 to 5 of each 21-day chemotherapy cycle. There will be no intrapatient dose modifications of G1T28 in Parts 2A and 2B of the study.

**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 dose of topotecan on a given day should not be greater than 4 hours.**

**G1T28 or placebo will only be administered with topotecan. If administration of topotecan 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, third, fourth, or fifth dose of G1T28 or placebo in any given cycle is not administered for any reason, do not administer the dose of topotecan 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, 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. [redacted]

Patients should meet the laboratory parameter requirements outlined in Section 10.4 before initiation of Cycle 2 and each subsequent cycle of topotecan. All nonhematologic drug-related toxicities (except alopecia) should have resolved to Grade 1 or baseline before initiation of the next cycle of topotecan.

## 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. Topotecan

Descriptions of the formulation of commercially-available topotecan 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 [redacted]

Individual vials of G1T28 will be labeled and supplied to the pharmacist/designee who will inventory the contents and document them according to the drug accountability requirements (Section 8.2.5).

8.2.2.2. Placebo

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

8.2.2.3. Topotecan

A description of the packaging and labeling of commercially-available topotecan 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

Commercially-available D5W or sodium chloride solution 0.9% will be stored per the manufacturer's specifications.

8.2.3.3. Topotecan

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

### 8.2.4. Procedure for Dispensing

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

### 8.2.5. Investigational Product Accountability

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

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) is open-label and there will be no randomization. Parts 2A and 2B are randomized and blinded. Patients meeting all inclusion and exclusion criteria in Parts 2A and 2B will be randomized 2:1 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

For G1T28, placebo, and topotecan dosing, the body surface area (BSA) calculation should use the actual body weight, not the ideal body weight. If a patient's weight fluctuates from visit to visit, the doses of G1T28 or placebo and topotecan can be adjusted at each visit, **OR** the dose need not be adjusted unless the change in actual body weight is ≥ 10%.

### 8.4.1. G1T28

The starting dose level for Part 1 will be 200 mg/m$^2$. See Section 6.1 for possible dose escalation/de-escalation decisions based on safety and PK data.

G1T28 diluted in 250 mL of D5W or sodium chloride solution 0.9% is to be administered by IV infusion over 30 (±5) minutes. If there is any study drug remaining in the G1T28 infusion bag at the end of the 30 (±5) minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. The infusion rate may be decreased to manage an infusion-related AE; for example, if a patient experiences a burning sensation during infusion, the infusion time may be increased to 45 minutes (or longer if clinically indicated) to alleviate the symptoms. 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 topotecan. If administration of topotecan 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 (±5) minutes. If there is any volume remaining in the infusion bag at the end of the 30 (±5) minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to protect the integrity of the blind. The

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

**The interval between doses of placebo on successive days should not be greater than 28 hours. Placebo will only be administered with topotecan. If administration of topotecan is discontinued, placebo will also be discontinued.**

### 8.4.3. Topotecan

The starting dose level of topotecan will be 1.5 mg/m$^2$ administered as an IV infusion over 30 (±5) minutes daily on Days 1 to 5 of each 21-day cycle. See Section 6.1 for possible dose adjustments based on safety and PK data.

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

**The interval between the dose of G1T28 or placebo and topotecan on a given day should not be greater than 4 hours.**

**Chemotherapy cannot be administered until after completion of the G1T28 or placebo infusion. If the second, third, fourth, or fifth dose of G1T28 or placebo in any given cycle is not administered for any reason, do not administer the dose of topotecan chemotherapy on that day, since this could potentially exacerbate myelosuppression (see Section 8.4.4.1).**

### 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/pharmacodynamic 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 Part 1 as described in Section 6.1.1) throughout the study**.

#### 8.4.4.2. Modification of Topotecan Dosing

Patients should meet the laboratory parameter requirements outlined in Section 10.4 before initiation of Cycle 2 and each subsequent cycle of topotecan. All nonhematologic

drug-related toxicities (except alopecia) should have resolved to Grade 1 or baseline before initiation of the next cycle of topotecan.

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 topotecan 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 and/or administrative reasons will lead to discontinuation of topotecan.

No more than 2 dose reductions in total are allowed for any patient. Toxicity that requires dose reduction more than twice will lead to discontinuation of topotecan. 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 Topotecan Dose Reductions**

| **Dose Level** | **Topotecan[a]** | | | |
|---|---|---|---|---|
| Starting Dose level | 1.5 mg/m$^2$ | 1.25 mg/m$^2$ | 1.0 mg/m$^2$ | 0.75 mg/m$^2$ |
| Dose level -1 (first dose reduction) | 1.25 mg/m$^2$ | 1.00 mg/m$^2$ | 0.8 mg/m$^2$ | 0.6 mg/m$^2$ |
| Dose level -2 (second dose reduction) | 1.00 mg/m$^2$ | 0.8 mg/m$^2$ | 0.65 mg/m$^2$ | 0.5 mg/m$^2$ |

a If the topotecan dose was adjusted in Part 1 (Section 6.1.1.4), Dose level -1 will consist of a 20% dose reduction from the adjusted Part 1 dose and Dose level -2 will consist of a 20% dose reduction from Dose level -1. Example dose reductions are shown for specified starting dose levels.

#### 8.4.4.2.1. 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 meet 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

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 Topotecan 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** | **Topotecan** |
|---|---|
| First episode | No change. Use G-CSF with subsequent cycles. Refer to the American Society of Clinical Oncology (ASCO) guidelines (Smith 2015). |
| Second episode | First dose reduction |
| Third episode | Second dose reduction |
| Fourth episode | Discontinue drug |
| **Platelet Count < 100 x $10^9$/L** | **Topotecan** |
| First episode | First dose reduction |
| Second episode | Second dose reduction |
| Third episode | 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 Topotecan Dose Adjustments Based on Absolute Neutrophil Count Nadir With or Without Fever**

| **Absolute Neutrophil Count Nadir** | **Topotecan** |
|---|---|
| **Grade 3 (without fever)** | 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 2015). |
| Second episode | First dose reduction |
| Third episode | Second dose reduction |
| Fourth episode | Discontinue drug |

| | |
|---|---|
| **Grade 3/4 with fever** | |
| First episode | No change. Use G-CSF with subsequent cycles. Refer to the ASCO guidelines (Smith 2015). |
| Second episode | First dose reduction |
| Third episode | Second dose reduction |
| Fourth episode | 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 Topotecan Dose Adjustment Based on Platelet Nadir**

| Platelet Count Nadir | Topotecan |
|---|---|
| **Grade 4 or ≥ Grade 3 with bleeding** | |
| First episode | First dose reduction |
| Second episode | Second dose reduction |
| Third episode | Discontinue drug |

Colony Stimulating Factors:

Use of **prophylactic** colony stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF]; granulocyte-macrophage colony-stimulating factor [GM-CSF]) **during Cycle 1** (ie, prior to the actual Cycle 2 Day 1 dosing visit) is **not allowed**. In subsequent cycles (Cycle 2 and beyond), prophylactic colony stimulating factors are allowed as outlined above in Table 8-2 and Table 8-3, which are based on the ASCO guidelines (Smith 2015) and package inserts (see Appendix 3). Note that colony stimulating factors should not be administered until at least 24 hours after the last dose of chemotherapy is administered in a given cycle. For example, if a patient has a neutropenic event in Cycle 1 that requires initiation of prophylactic G-CSF in Cycle 2, the G-CSF should not be started until 24 hours after the last dose of topotecan in Cycle 2.

If in any cycle (including Cycle 1), a patient experiences febrile neutropenia and is at high risk for infection-associated complications OR has prognostic factors that are predictive of poor clinical outcomes (Table 8-5), colony stimulating factors may be used to treat the febrile neutropenia event per the ASCO guidelines and package insert.

**Table 8-5 Patient Risk Factors for Poor Clinical Outcomes Resulting from Febrile Neutropenia or Infection**

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

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

Erythropoietin stimulating agents (ESAs):

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

8.4.4.2.2. Dose Modifications for Nonhematologic Drug-Related Toxicity

Hepatic Toxicity

The following dose adjustments for topotecan are based on serum AST/ALT and bilirubin levels (Table 8-6) during the preceding treatment cycle.

**Table 8-6 Topotecan Reduction for Hepatic Toxicity**

| AST/ALT | | Bilirubin | Topotecan |
|---|---|---|---|
| Grade 1 | and/ or | ≤ Grade 2 | No change |
| ≥ Grade 2[a] | and/or | ≥Grade 3 | |
| First episode | | First episode | First dose reduction |
| Second episode | | Second episode | Second dose reduction |
| Third episode | | Third episode | 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 anti-emetic 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 rechallenged, 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 at a low rate (20 mg/hour) after recovery of symptoms. 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 topotecan 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, then epinephrine is recommended. Patient should not receive any further doses of topotecan. 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 topotecan. 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 topotecan.

## 8.5. Randomization and Blinding

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

Parts 2A and 2B are randomized and blinded. Patients meeting all inclusion and exclusion criteria in Parts 2A and 2B will be randomized 2:1 to receive G1T28 or placebo by an interactive web response system (IWRS) according to a randomization schedule generated by an unblinded statistician. Randomization will be stratified on the basis of ECOG performance status (0 to 1 versus 2) and sensitivity to first-line treatment (sensitive: CR, PR, or SD after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: PD as best response to first-line therapy or progression-free interval < 90 days after completion of first line therapy). 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 first dose of study drug, 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. This includes any low-dose systemic chemotherapeutic agent given for a nononcologic purpose (eg, low-dose methotrexate for rheumatoid arthritis).

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.

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

Necessary supportive care such as antiemetics, antidiarrheals, etc., per the standard of care at the study center will be permitted. See Section 8.4.4.2.1 for guidance on the use of growth factors (colony stimulating factors and ESAs) during the study. 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). Since G1T28 has been shown to inhibit renal transporters for which topotecan is a substrate, there is a potential for increasing topotecan exposure when administered after G1T28 (see Section 4.3.2). However, the relative contribution of these transporters in topotecan clearance has not been established. Therefore, in Part 1 of the study, PK of G1T28 and topotecan will be assessed on Days 1 and 4 of the first cycle and any recommendations for dose modifications will be made by the SMC based on safety and PK data (Section 6.1.1.4).

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).

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

## 8.8. Treatment Compliance

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

| | Screening | Enroll | Cycle 1 and Odd Cycles[a] (21 days) | | | | | | | | Cycle 2 and Even Cycles[a] (21 days) | | | | | | | | Last Cycle | Post-Treatment Visit[b] | Survival Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Day** | **-14** | **-3 to 1** | **1** | **2** | **3** | **4** | **5** | **10** | **12** | **15** | **1** | **2** | **3** | **4** | **5** | **10** | **12** | **15** | **22** | **30 +3** | |
| 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[g] | | | | | | | X | | X | |
| Hematology | X | | X[h] | | | | X | X | X | X[s] | X[h] | | | | X | X | X | X[s] | X | X | |
| Urinalysis | X | | X[g] | | | | | | | | X[g] | | | | | | | | | X | |
| Immunologic markers[i] | | | X | | | | | | | X | X | | | | | | | X | X | X | |
| ECG[j] | X | | X[j] | | | X[j] | | | | | | | | | | | | | | X | |
| Pregnancy test[k] | X | | X | | | | | | | | X | | | | | | | | | | |
| Randomization[r] | | X | | | | | | | | | | | | | | | | | | | |
| Tumor Assessment[l] | X[l2] | | | | | | | | | | | | | | | | | X | | X[l1, l2] | X[l1] |
| Tumor Testing[m] | | X | | | | | | | | | | | | | | | | | | | |
| PK[n] | | | X | | | X | | | | | | | | | | | | | | | |
| G1T28 or placebo[o] | | | X | X | X | X | X | | | | X | X | X | X | X | | | | | | |
| Topotecan | | | X | X | X | X | X | | | | X | X | X | X | X | | | | | | |

| | Screening | Enroll | Cycle 1 and Odd Cycles[a] (21 days) | | | | | | | | Cycle 2 and Even Cycles[a] (21 days) | | | | | | | | Last Cycle | Post-Treatment Visit[b] | Survival Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cycle Day | -14 | -3 to 1 | 1 | 2 | 3 | 4 | 5 | 10 | 12 | 15 | 1 | 2 | 3 | 4 | 5 | 10 | 12 | 15 | 22 | 30 +3 | |
| [redacted] | | | [redacted] | | | | | [redacted] | | | [redacted] | | | | | [redacted] | | | | [redacted] | |
| AEs[q] | X | X | | | | | | | | | | | | | | | | | | | |
| Prior and Con. Medications | X | X | | | | | | | | | | | | | | | | | | | |
| Survival Follow-up[c] | | | | | | | | | | | | | | | | | | | | | X |

AE = adverse event; ECG = electrocardiogram; [redacted] val. = evaluation; PK = pharmacokinetic

a G1T28 + topotecan will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. 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. Any anticancer therapies used will be collected. Patients will be followed for survival until at least 50% of the patients in Parts 2A and 2B 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.

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, documentation of tumor diagnosis, baseline signs and symptoms within 4 weeks prior to the first dose of study drug, weight loss in the 6 months prior to the first dose of study drug (≤ 5% or > 5%), and medications taken within 14 days prior to the first dose of study drug

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

g Clinical chemistry will be obtained (albumin, alkaline phosphatase [ALP], 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 + topotecan.

h Hematology will be obtained (hemoglobin, hematocrit, white blood cells (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 + topotecan.

i [redacted]

j Patients participating in Part 1 of the study will have ECGs completed at the following time points on Days 1 and 4 of Cycle 1: predose, 0.5 hour (end of infusion [EOI] of G1T28), 1 hour (± 10 minutes), and 6.5 hours (± 15 minutes) after start of G1T28 infusion. Patients participating in Parts 2A and 2B of the study will have ECGs completed at the following time points on Day 4 of Cycle 1: predose, 0.5 hour (EOI of G1T28), 1 hour (± 10 minutes), and between 3.5 to 6.5 hours (± 15 minutes) after start of G1T28 infusion.

k For female patients of childbearing potential, serum ß-hCG at screening; serum or urine ß-hCG, obtained up to 72 hours prior to each dose of G1T28 + topotecan chemotherapy in each cycle

l For tumor assessment, all sites of disease (including brain metastases, if present at screening) 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 may 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 PET is used, it should also be accompanied by spiral CT or MRI.

l1: 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 of treatment discontinuation). For those patients in the survival follow-up who have not progressed at the time of study drug discontinuation, tumor assessments, including all sites of disease, will be assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.

l2: Brain scans with contrast (by CT or MRI) to be obtained with tumor assessment at screening (within 28 days of dosing). For those without brain metastases at screening, an additional scan should be performed at the Post-Treatment Visit for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks of treatment discontinuation). For those with brain metastases, brain scans should be done with each tumor assessment.

m [redacted]

n Patients enrolled in Part 1 will have G1T28 and topotecan PK samples collected on Days 1 and 4 (as applicable) of Cycle 1 at the time points specified in Section 11.2. In addition, limited PK samples will be collected on Cycle 1 Day 4 in Parts 2A and 2B of the study for G1T28 population PK analysis. Blood samples will be collected in Parts 2A and 2B of the study at the time points specified in Section 11.2.

o G1T28 or placebo will be administered as an IV infusion in 250 mL of D5W or sodium chloride solution 0.9% over 30 (± 5) minutes prior to topotecan chemotherapy on Days 1 to 5 of every cycle (see Section 8.1). If there is any study drug remaining in the G1T28 infusion bag at the end of the 30 (± 5) minutes, the infusion should be continued at the same rate until the entire contents of the bag have been administered to ensure patients receive the full dose. The interval between doses of G1T28 on successive days should not be greater than 28 hours. The interval between the dose of G1T28 and the dose of topotecan on a given day should not be greater than 4 hours. G1T28 will only be administered with topotecan. If administration of topotecan is discontinued, G1T28 should also be discontinued. Chemotherapy cannot be administered until after completion of the G1T28 infusion. If the second, third, fourth, or fifth dose of G1T28 in any given cycle is not administered for any reason, do not administer the dose of topotecan 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 PRO (scales), CBC assessment on Day 22, the Post-Treatment Visit, and the Survival Follow-up Phase of the study.

p 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 + topotecan. Patient-reported outcomes may be obtained up to 24 hours prior to the first dose of each cycle of G1T28 + topotecan.

q 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.

r For patients enrolled in Parts 2A and 2B, randomization is to be done within 3 days prior to the first dose of G1T28 or placebo + topotecan, following confirmation that the patient is eligible for the study.

s Patients with an ANC $< 0.5 \times 10^9$/L on Day 15 shall be followed (eg, every 24 to72 hours) for recovery (to ensure that duration of ANC $< 0.5 \times 10^9$/L does not exceed 7 days).

# 10. SCHEDULE OF STUDY PROCEDURES

Study procedures are summarized across all study visits within the schedule of assessments (Table 9-1). Parts 1, 2A, and 2B 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 (Parts 2A and 2B), and the start of study treatment. Eligible patients will be instructed on all protocol requirements, including any restrictions on concomitant medication usage.

Archived tumor samples should be sent to a central pathology laboratory to confirm the diagnosis of SCLC. [redacted] 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. [redacted]

[redacted]

## 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 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)
- CD4/CD8 immunologic markers (as applicable)
- Electrocardiogram (predose, **Cycle 1 in Part 1 only**)
- Plasma PK sample (predose, **Cycle 1 in Part 1 only**)
- Pregnancy test (note: may be obtained up to 72 hours prior to the first dose of each cycle)
- [redacted]

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

Patients that still meet all of the eligibility criteria will begin treatment Cycle 1. The first dose of study treatments (G1T28 or placebo + topotecan) 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 and topotecan infusions; only needed once between infusions)
- Electrocardiogram (0.5 hour [end of infusion (EOI) of G1T28 or placebo], 1 hour (± 10 minutes), and 6.5 hours (± 15 minutes) after the start of G1T28 or placebo infusion, **Cycle 1 in Part 1 only**).
- Plasma PK samples (postdose samples as described in Section 11.2, **Cycle 1 in Part 1 only**)

Cycle 1 Days 2, 3, 4, 5, 10, 12, and 15

All procedures and assessments to be conducted during Days 2, 3, 4, 5, 10, 12, and 15 of Cycle 1 are outlined in Table 9-1. The DMC may recommend decreasing the frequency of

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

At Days 2, 3, 4, and 5, study treatments (G1T28 or placebo + topotecan) will be administered (as described in Section 8.1).

At Day 4 in Cycle 1 of Parts 1, 2A, and 2B, the following additional assessments will be performed:

- Electrocardiogram (predose, 0.5 hour [EOI of G1T28 or placebo], 1 hour [± 10 minutes], and 6.5 hours [± 15 minutes] after start of G1T28 or placebo infusion in Part 1 of the study; and predose, 0.5 hour [EOI of G1T28 or placebo], 1 hour [± 10 minutes], and between 3.5 to 6.5 hours [± 15 minutes] after start of G1T28 or placebo infusion in Parts 2A and 2B of the study)
- Plasma PK sample (predose and postdose samples as described for Parts 1, 2A, and 2B of the study 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 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)
- CD4/CD8 immunologic markers (as applicable)
- Pregnancy test (note: may be obtained up to 72 hours prior to the first dose of each cycle)
- [redacted]

Vital signs should be obtained immediately before and after G1T28 or placebo and topotecan infusions; only needed 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 $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline. Dose modifications based on lack of recovery to these absolute neutrophil and platelet counts on the first day of treatment for Cycle 2 are outlined in Table 8-2. A delay of up to 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 Section 6.1.4, a delay of up to 1 week is permitted for administrative reasons (eg, holiday, vacation, etc.). [redacted]

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 + topotecan) will be administered as described in Section 8.1.

Cycle 2 Days 2, 3, 4, 5, 10, 12, and 15

All procedures and assessments to be conducted during Days 2, 3, 4, 5, 10, 12, and 15 of Cycle 2 are outlined in Table 9-1. The DMC may recommend decreasing the frequency of hematological evaluations based on accumulating data. The investigators and IRBs or IECs will be notified if the frequency is reduced.

For Cycle 2 Day 2 through Day 5, study treatments (G1T28 or placebo + topotecan) will be administered as described in Section 8.1.

For tumor assessment, all sites of disease (including brain metastases, if present at screening) 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 $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and nonhematologic drug-related toxicities (except alopecia) must be $\leq$ Grade 1 or have returned to baseline. Dose modifications based on lack of recovery to these absolute neutrophil and platelet counts on the first day of treatment for 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 Section 6.1.4, 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 PRO scales, CBC and CD4/CD8 immunologic marker (as applicable) assessments on Day 22, return for the Post-Treatment Visit, and the Survival Follow-up Phase of the study, which is to continue until at least 50% of the patients in Parts 2A and 2B have died.

## 10.6. Post-Treatment Visit

Patients will return to the study center for a Post-Treatment Visit at 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
- CD4/CD8 immunologic markers (as applicable)
- 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])
- [redacted]

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 in Parts 2A and 2B 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

### 10.8. Details of any anticancer treatment 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 completion of the 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 patients in Parts 2A and 2B 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; [redacted]. 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 topotecan will be assessed using the NCI CTCAE, Version 4.03.

## 11.2. Pharmacokinetic Assessments

In Parts 1, 2A, and 2B of the study, serial blood samples (5-mL samples) will be collected for measurement of G1T28 and topotecan 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 and topotecan using a validated method. Any remaining sample may be stored long term for the future analysis of G1T28 drug metabolites.

**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 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 topotecan), 1.5, 2, 2.5, 3, 4.5, 6.5, 8.5 (optional time point, if approved by the sponsor in advance), and 24.5 hours postdose (prior to G1T28 dose on Day 2). Blood samples collected at the following time points are relative to the start of G1T28: 1.5 to 24.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. The EOI sample for topotecan 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 start 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 start of G1T28 infusion. A ± 1-hour time window will be allowed for the 24.5 hours after the start 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 and Topotecan**

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

EOI = end of infusion; h = hour; Topo = topotecan

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

### Part 1: Cycle 1 Day 4

Blood samples will be collected at the following time points on Cycle 1 Day 4 for all patients enrolled in Part 1 of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (EOI of G1T28), 1 (EOI of topotecan), 1.5, 2, 2.5, 3, 4.5, 6.5, 8.5 (optional time point, if approved by the sponsor in advance), and 24.5 hours postdose (prior to G1T28 dose on Day 5). Blood samples collected at the following time points are relative to the start of G1T28: 1.5 to 24.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. The EOI sample for topotecan 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 1also apply to Cycle 1 Day 4. The Cycle 1 Day 4 sampling scheme is summarized in Table 11-2.

**Table 11-2 Part 1: Day 4 of Cycle 1 Blood Sampling Scheme Based on Predicted Administration Times of G1T28 and Topotecan**

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

EOI = end of infusion; h = hour; Topo = topotecan

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

### Parts 2A and 2B: Cycle 1 Day 4

Limited PK samples will be collected on Cycle 1 Day 4 in Parts 2A and 2B of the study for population PK analysis. Blood samples will be collected at the following time points relative to the start of G1T28 infusion on Cycle 1 Day 4 for all patients enrolled in Parts 2A and 2B of the study: predose (0 hour; prior to dosing of G1T28) and at 0.5 (EOI of G1T28), 1 (EOI of topotecan), between 3 to 4 hours and between 5.5 to 6.5 hours. The EOI sample for G1T28 should be drawn 2 to 5 minutes prior to the EOI. A ± 5-minute time window will be allowed for samples collected predose and 1 hour after the end of G1T28 infusion. A ± 10-minute time window will be allowed for samples collected between 3 to 6.5 hours from the start of G1T28 infusion.

**Pharmacokinetic Parameters**

Pharmacokinetic parameters to be derived from G1T28 and topotecan 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 |
| $\lambda_z$ | 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 $\lambda_z$ |
| $AUC_{0-\infty}$ | Area under the concentration-time curve from time-zero extrapolated to infinity, calculated as: $AUC\,\text{inf} = AUClast + \frac{Clast}{\lambda z}$ where $C_{last}$ is the last quantifiable concentration in the terminal elimination phase. |
| CL | Clearance after intravenous administration, calculated as: $CL = \frac{Dose}{AUC_{\text{inf}}}$ |
| Vz | Volume of distribution in the terminal elimination phase, calculated as: $Vz = \frac{CL}{\lambda z}$ |

## 11.3. 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.

Adverse events include the following:

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

An AE does not include:

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

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

- An unexpected ADR is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product). All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an

AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. All serious and unexpected ADRs will have expedited reporting to the regulatory agencies following the International Conference on Harmonisation (ICH) requirements

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

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

11.3.1.2. 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 + topotecan. 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. If the EDC system is not operational, the paper SAE Form must be completed within 24 hours and faxed to the number below.

**PPD Pharmacovigilance:**
**EMEA/APAC 24 Hour Safety Hotline: +44 1223 374 240**
**24 Hour Safety Hotline Fax: +44 1223 374 102**

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

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

#### 11.3.1.12. Infusion-Related Reactions

An infusion-related reaction is defined as "an adverse reaction to the infusion of pharmacological or biological substances" and can be divided into 2 categories: local effects and systemic effects (CTCAE, Version 4.03). Those AEs that are infusion-related should be recorded in the eCRF as "infusion-related reactions." Any associated symptoms as outlined in Table 11-4 below should also be recorded as AEs. The associated symptoms and details (ie, local versus systemic) will also be captured on the infusion/dosing page in the EDC system.

**Table 11-4 G1T28-03: Infusion-Related Reaction Symptoms**

| | | |
|---|---|---|
| Redness | Pyrexia | Hoarseness |
| Edema | Angioedema | Hypoxia |
| Ulceration | Flushing | Mouth tingling |
| Pain | Rigors/chills | Diaphoresis |
| Phlebitis | Bronchospasm/wheezing | Rash (nonspecific) |
| Warmth | Chest pain | Syncope |
| Pruritis | Back pain | Tachycardia |
| Hypotension | Difficulty swallowing | Throat tightness |
| Shortness of breath/dyspnea | Facial swelling | |

#### 11.3.1.13. Handling of Overdoses and Toxicity

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

#### 11.3.1.14. Reporting of Pregnancies

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

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

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, WBCs with differential and platelet counts)
- Chemistry (albumin, 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)

Patients with an ANC $< 0.5 \times 10^9$/L on Day 15 shall be followed (eg, every 24 to72 hours) until ANC is at least $> 0.5 \times 10^9$/L (to ensure the duration of ANC $< 0.5 \times 10^9$/L does not exceed 7 days).

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 remeasured 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 or IECs 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. 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. 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. [redacted]

## 11.5. Tumor Response

### 11.5.1. Tumor Assessments

For tumor assessment, all sites of disease (including brain metastases, if present at screening) should be assessed radiologically by CT or MRI (with contrast unless not clinically appropriate) at screening and after every even cycle, until the occurrence of disease progression (see Table 9-1). Brain scans with contrast (by CT or MRI) should be obtained with tumor assessments at screening (within 28 days of dosing). For patients without brain

metastases at screening, an additional scan should be performed at the Post-Treatment Visit for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks of treatment discontinuation). For those with brain metastases at baseline, brain scans should be done with each tumor assessment.

CT or MRI scans obtained prior to informed consent will not need to be repeated if performed within 14 days prior to dosing. Brain MRI or CT scans obtained prior to informed consent will not need to be repeated if performed within 28 days prior to dosing. Assessments should be performed within 7 days 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. Assessments may be performed within 7 days of starting the subsequent cycle. 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, within 4 weeks of study drug discontinuation and then 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 11-5 describes the evaluation of overall response at each time point based on target and nontarget lesion responses at each time point, as well as the appearance of new lesions. The best overall response is the best response recorded from the start of the treatment until disease progression. Confirmation of CR and PR is required as described in Sections 11.5.3.1 and 11.5.3.2.

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

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

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

## 11.6. [redacted]

[redacted]

## 11.7. Immunologic Markers (Optional)

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 cell subsets will be characterized in patients enrolled into the study and who agree to participate in this optional portion of the study.

[redacted]

## 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 topotecan 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
- Treatment delay greater than 2 weeks
- 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 progressive disease 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). For any differences in analyses between the protocol and SAP, the plan as outlined in the SAP will supersede the protocol.

## 13.1. Sample Size and Power

Approximately 40 patients will be enrolled in Part 1 of the study (dose ranging), approximately 45 patients will be enrolled in Part 2A of the study, and approximately 45 patients will be enrolled in Part 2B of the study. The Part 1 sample size is based on standard sample size for dose escalation to determine a tolerable G1T28 dose administered prior to topotecan on Days 1 to 5 of 21-day cycles. In Part 2 of the study, approximately 90 patients will be enrolled into 3 groups (G1T28 + topotecan 0.75 mg/m$^2$, G1T28 + topotecan 1.5 mg/m$^2$, and placebo + topotecan 1.5 mg/m$^2$). With 30 patients per group, the precision for point estimates in each group is as follows: the 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals are at most the observed proportion ± 0.167; and the 95% CI width for continuous endpoints using the t-distribution are the observed mean ± 0.373*standard deviation of the endpoint. Moreover, as there are approximately 130 patients for all data from Part 1, Part 2A, and Part 2B; the precision for point estimates is as follows: the 95% CI width for binary endpoints based on Wilson score intervals are at most the observed proportion ± 0.081; and the 95% CI width for continuous endpoints using the t-distribution are the observed mean ± 0.174*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. 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. 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 Parts 2A and 2B of the study.

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

### 13.2.2. Timing of Analyses

Recent clinical results from Study G1T28-02 in patients with treatment-naïve extensive-stage SCLC comparing trilaciclib plus etoposide/carboplatin to placebo + etoposide/carboplatin, provided compelling evidence that trilaciclib decreased myelosuppression across three

lineages: neutrophils, red blood cells and lymphocytes and achieved a meaningful level of myelopreservation. While this trial was specifically designed to evaluate myelosuppression endpoints in SCLC patients receiving topotecan, the current design requires all patients to complete treatment prior to unblinding and analysis. Since patients in this trial may be treated indefinitely, i.e. until progression of disease, unacceptable toxicity etc, it is not possible to definitively predict when unblinding and analysis may occur. Therefore, an additional analysis (as described below) is to be added in this protocol amendment, which will enable evaluation of myelosuppression endpoints prior to all patients discontinuing treatment. The timing of the analysis has been chosen to (1) ensure that all patients will have had the opportunity to receive at least 12 weeks (4 cycles) of topotecan with the majority having completed therapy, and (2) that the myelopreservation results will be sufficiently mature such that the data generated by any patients still on trial will not alter the overall myelopreservation conclusions in a clinically meaningful way.

#### 13.2.2.1. Interim Safety Reviews

A SMC will review safety and PK of G1T28 and topotecan for all patients enrolled in Part 1 of the study. The SMC will consist of the clinical investigator(s), the medical monitor, and G1 Therapeutics representatives and/or designees. The committee will make recommendations for dose escalation/de-escalation based on the criteria listed in Sections 6.1.1.1 to 6.1.1.4.

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 Parts 2A and 2B, depending upon the enrollment rate. Additional reviews may occur based on DMC requests. The committee will consist of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, SCLC) and biostatistics. These individuals will be entirely independent of the conduct of the study.

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

#### 13.2.2.2. Final Myelopreservation Analysis and Interim Anti-Tumor Efficacy Analysis

A final analysis for myelopreservation endpoints, and the first interim analysis for anti-tumor efficacy endpoints (including response rate, PFS and OS), will be performed after all patients have had the opportunity to receive at least 12 weeks (4 cycles) of treatment. At the time of this final analysis, the Sponsor will be unblinded, however investigators and patients will remain blinded.

#### 13.2.2.3. Final analysis and End of Study Analysis

The final anti-tumor efficacy analysis will coincide with the end of study analysis which will occur after at least 50% of patients have died. Additional anti-tumor efficacy analyses may be done with the timing to occur between the first interim anti-tumor efficacy analysis and the final anti-tumor efficacy analysis.

### 13.2.3. General Considerations for Data Analysis

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

Data will be summarized descriptively by dose level, if applicable, and overall. Patients with the same dose level (Phase 2 dose level) in Parts 1, 2A, and 2B will be summarized together, unless described otherwise. In that case, patients with the same dose level will be summarized at the Phase 2 dose level together and separately by study part (Parts 1, 2A, and 2B). 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. 95% confidence intervals will be presented for efficacy [redacted] endpoints.

The effects of covariates (eg, ECOG, extent of prior chemotherapy, prior response to chemotherapy) 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. [redacted]

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

Disposition, demographics, and baseline characteristics will be summarized descriptively. Summaries will be done overall, by dose level, and separately by study part (Parts 1, 2A, and 2B) for summaries at the Phase 2 dose level.

## 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 dose reductions 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

- [redacted]

### 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 Parts 2A and 2B, 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), sensitivity to first-line treatment (sensitive: CR, PR, or SD after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: PD as best response to first-line therapy or progression-free interval < 90 days after completion of first line therapy), 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, ECOG at entry, and sensitivity to first-line treatment (sensitive: CR, PR, or SD after first-line therapy and recurrence- or progression-free interval ≥ 90 days after completion of first-line therapy versus resistant to first line treatment: PD as best response to first-line therapy or progression-free interval < 90 days after completion of first line therapy). The unstructured covariance model will be used to tabulate the LS means for each treatment group and the LS mean difference between treatment groups at each cycle. Two-sided 95% CIs will be constructed around the LS mean differences in AUC between treatment groups. An analysis accounting for cumulative dose exposure at each cycle will be performed to support the evaluation of AUC over cycles.

The proportion of patients whose blood counts 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 Parts 2A and 2B, 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 Parts 2A and 2B, 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.

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

Hematologic recovery will be defined in the SAP. The number and percentage of patients with hematologic recovery will be calculated at each cycle. Time to postdose recovery within a cycle will be estimated using the Kaplan-Meier method.

#### 13.4.2.3. Analysis of Chemotherapy Exposure and Compliance

The following parameters will be summarized: total duration of treatment, total number of cycles received, cumulative dose of topotecan received, and number and percentage of patients experiencing one or more dose delay, interruption, and reduction. Summaries of exposure will be done overall, by dose level, and separately by study part (Parts 1, 2A, and 2B) for summaries at the Phase 2 dose level.

The following parameters will be summarized for each cycle and overall: number and percentage of patients receiving any dose of chemotherapy, experiencing one or more dose delay, interruption, and reduction, and cumulative dose of topotecan received. The number and percentage of patients experiencing a dose reduction or treatment cycle delay due to a hematologic toxicity will also 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 Parts 2A and 2B, 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.

13.4.2.5. [redacted]

[redacted]

[redacted]

A [redacted]

[redacted]

## 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 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 nor had documented disease progression at the time of analysis will be censored on the last on-study date with nonmissing tumor response data.

Overall survival is measured from 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 rules for the analysis of PFS and OS data will be described in the SAP.

## 13.6. [redacted]

[redacted]

[redacted]

## 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 4 of Cycle 1 to determine G1T28 and topotecan 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.

[redacted]

## 13.8. Immunologic Markers

To evaluate the impact of G1T28 administration on chemotherapy-induced changes of the immune system, peripheral blood immune cell subsets will be characterized in patients who agree to participate in this optional portion of the study. The immunophenotypic change from baseline will be listed and summarized, if data warrant.

[redacted]

# 14. QUALITY CONTROL AND QUALITY ASSURANCE

An eCRF must be completed for each patient enrolled. Each completed eCRF, as well as records for those patients who discontinue the study, will require a signature by the principal investigator or designee (subinvestigator) 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 IEC 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 or IEC prior to initiating the study. Approval must be obtained in writing via a letter identifying the protocol, the date of the IRB or IEC meeting, and the date of approval. Any modifications made to the protocol after receipt of the IRB or IEC approval must also be submitted by the investigator to the IRB or IEC in accordance with local procedures and regulatory requirements. Any updates to the protocol should receive IRB or IEC approval or favorable opinion, which should be documented in a letter to the investigator, prior to implementation.

## 15.3. Informed Consent

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

## 15.4. Patient Confidentiality

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

## 15.5. Adherence to the Protocol

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

## 15.6. Protocol Amendments

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

All protocol modifications must be submitted to the appropriate IRB or IEC 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 or IEC in writing of the study's completion or early termination. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

# 16. DATA HANDLING AND RECORD KEEPING

## 16.1. Data Collection and Retrieval

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

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

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

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

## 16.2. Data Monitoring Committee

An external DMC will be used to evaluate safety of Parts 2A and 2B 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 or IEC of study closure. Such updates and notifications are the responsibility of the investigator.

## 16.4. Records Retention

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

Patient clinical source documents may include (but not limited to) patient hospital records, physician's and nurse's notes, original laboratory reports, ECG, 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.

# 18. REFERENCES

Apetoh L, Ghiringhelli F, Tesniere A, et al. The interaction between HMGB1 and TLR4 dictates the outcome of anticancer chemotherapy and radiotherapy. *Immunol Rev*. 2007 Dec;220:47-59.

Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. *Cell Death Differ*. 2014 Jan;21(1):15-25.

Cagle PT, el-Naggar AK, Xu HJ, Hu SX, Benedict WF. Differential retinoblastoma protein expression in neuroendocrine tumors of the lung. Potential diagnostic implications. *Am J Pathol.* 1997;150:393-400.

Casares N, Pequignot MO, Tesniere A, et al. Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death. *J Exp Med*. 2005 Dec 19;202(12):1691-1701.

Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer*. 1995 Jun;12(3):199-220.

D'Amico D, Carbone D, Mitsudomi T, et al. High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumors. *Oncogene*. 1992;7:339-346.

Eckhardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol*. May 2007;25(15):2086-2092.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.

Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther*. 2004 Nov;3(11):1427-1438.

Gallo JM, Laub PB, Rowinsky EK, Grochow LB, Baker SD. Population pharmacokinetic model for topotecan derived from Phase 1 clinical trials. *J Clin Oncol*. 2000; 18:2459-2467.

Gerrits CJ, Burris H, Schellens JH, et al. Five days of oral topotecan (Hycamtin), a phase I and pharmacological study in adult patients with solid tumours. *Eur J Cancer*. 1998;34(7):1030-1035.

Gouyer V, Gazzeri S, Brambilla E, et al. Loss of heterozygosity at the RB locus correlates with loss of RB protein in primary malignant neuro-endocrine lung carcinomas. *Int J Cancer.* 1994;58:818-824.

Grochow LB, Rowinsky EK, Johnson R, et al. Pharmacokinetics and pharmacodynamics of topotecan in patients with advanced cancer. *Drug Metab Dispos.* 1992;20(5):706-713.

Heighway J, Betticher DC. Lung: small cell cancer. *Atlas of Genetics and Cytogenetics in Oncology and Haematology*. June 2004 URL : http://atlasgeneticsoncology.org/Tumors/LungSmallCellID5142.html.

Herben VM, ten Bokkel Huinink WW, Beijnen JH. Clinical pharmacokinetics of topotecan. *Clin Pharmacokinet*. 1996;31(2):85-102.

McDonnell AM, Nowak AK, Lake RA. Contribution of the immune system to the chemotherapeutic response. *Semin Immunopathol*. 2011 Jul;33(4):353-367.

Molina JR, Kaufmann SH, Reid JM, et al. Evaluation of lapatinib and topotecan combination therapy: tissue culture, murine xenograft, and Phase I clinical trial data. *Clinical cancer research*. 2008;14(23):7900-7908.

Montazeri A, Culine S, Laguerre B, et al. Individual adaptive dosing of topotecan in ovarian cancer. *Clin Cancer Res*. 2002;8:394-399.

Mould DR, Nicholas HG, Holford MB, et al. Population pharmacokinetic and adverse event analysis of topotecan in patients with solid tumors. *Clin Pharmacol Ther*. 2002;71:334-348.

O'Reilly S, Rowinsky EK, Slichenmyer W, et al. Phase I and pharmacologic study of topotecan in patients with impaired renal function. *J Clin Oncol.* Dec 1996a;14(12):3062-3073.

O'Reilly S, Rowinsky E, Slichenmyer W, et al. Phase I and pharmacologic studies of topotecan in patients with impaired hepatic function. *J Natl Cancer Inst*. Jun1996b;88(12):817-824.

Peifer M, Fernandez-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet*. 2012;44:1104-1110.

Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res*. 2009 Jul 1;69(13):5383-5391.

Rudin CM, Durinck S, Stawiski EW, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat Genet*.2012;44:1111-1116.

Saltz L, Sirott M, Young C, et al. Phase 1 clinical and pharmacology study of topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor. *J Natl. Cancer Inst*. 1993;85:1499-1507.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence based clinical practice guideline. *J Clin Oncol*. 2006 Jul 1;24(19):3187-3205.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2015 Oct 1; 33(28): 3199-3212.

Stewart CF, Tagen M, Schwartzberg LS, Blakely LJ, Tauer KW, Smiley LM. Phase I dosage finding and pharmacokinetic study of intravenous topotecan and oral erlotinib in adults with refractory solid tumors. *Cancer Chemother Pharmacol*. 2014 Mar;73(3):561-568.

Tanihara Y, Masuda S, Sato T, Katsura T, Ogawa O, Inui K. Substrate specificity of MATE1 and MATE2-K, human multidrug and toxin extrusions/H(+)-organic cation antiporters. *Biochem Pharmacol*. Jul 2007; 74(2):359-371.

van Warmerdam LJC, Verweij J, Schellens JHM, et al. Pharmacokinetics and pharmacodynamics of topotecan administered daily for 5 days every 3 weeks. Cancer Chemother Pharmacol. 1995;35:237-245.

von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol*. Dec 2014;32(35):4012-4019.

Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*. 1997 Feb;13(2):63-74.

Yuan J, Knorr J, Altmannsberger M, et al. Expression of p16 and lack of pRB in primary small cell lung cancer. *J Pathol*. 1999;189:358-362.

Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. *Nat Rev Immunol*. 2008 Jan;8(1):59-73.

# 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 Insert for Chemotherapy Agent

Hycamtin® (topotecan hydrochloride) package insert link:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020671s020lbl.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