Phase 1b/2 Safety, Pharmacokinetic, and Efficacy Study of G1T38 in Combination with Osimertinib in Patients with EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

Clinical Study Protocol G1T38-03
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Investigational Phase: 1b/2

Sponsored by:
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I have read and understand the contents of this clinical protocol, Version 4.0 for Study G1T38-03 dated 02 September 2019 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], G1 Therapeutics

PROTOCOL SIGNATURE PAGE

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

Principal Investigator:

Principal Investigator Signature	Date
Principal Investigator Name	Institution

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
β-hCG	beta human chorionic gonadotropin
BOR	best overall response
CBC	complete blood count
CBR	clinical benefit rate
CDK4/6	cyclin-dependent kinase 4/6
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent oral clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
EC_{50}	50% effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ER	estrogen receptor
FDA	Food and Drug Administration

Abbreviation	Definition
FDG-PET	positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose
FGFR	fibroblast growth factor receptor
FIH	first-in-human
G1	gap 1 phase of the cell cycle
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEMM	genetically engineered mouse model
HDPE	high-density polyethylene
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go related gene
HR	hormone receptor
HRCT	high-resolution computed tomography
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IGF1R	insulin-like growth factor 1 receptor
ILD	interstitial lung disease
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web-response system
LD	longest diameter
LVEF	left ventricular ejection fraction
MATE1 or 2-K	multidrug and toxin extrusion 1 or 2-K
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
NTL	nontarget lesion
NYHA	New York Heart Association
OCT1 or 2	organic cation transporter 1 or 2

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
PTV	Post-Treatment visit
QTc	QT interval corrected for heart rate
Rb	retinoblastoma protein
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
S	synthesis phase of cell cycle in which DNA is replicated
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMC	safety monitoring committee
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution during the terminal phase
WHO	World Health Organization

3. SYNOPSIS

Title	Phase 1b/2 Safety, Pharmacokinetic, and Efficacy Study of G1T38 in Combination with Osimertinib in Patients with EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)
Study Rationale	Non-small cell lung cancers (NSCLCs) represent the vast majority of lung cancers around the world, and epidermal growth factor receptor (EGFR) mutations occur in approximately 15% of NSCLCs in the United States and up to 62% of NSCLCs in Asia. Osimertinib (Tagrisso®) has been established as the second-line standard of care in EGFR-positive NSCLC with a T790M mutation after failure of a first-line EGFR tyrosine kinase inhibitor (TKI), and has also recently demonstrated benefit in first-line EGFR-positive NSCLC regardless of T790M status. Historical median progression-free survival (PFS) with second-line osimertinib monotherapy is approximately 10 months, and the overall response rate (ORR) is approximately 70%. Nearly all patients eventually develop resistance to osimertinib and experience disease progression. The putative resistance mechanisms to osimertinib include activating mutations in PIK3CA, MEK1, and KRAS; amplifications in MET, HER2, and FGFR1; activation of the IGF1R pathway; and EGFR C797S mutation. Many of these are upstream of cyclin-dependent kinase 4/6 (CDK4/6), suggesting that combining G1T38 with osimertinib has the potential to block these resistance pathways, delay the time to resistance, prolong PFS, and thus delay the need for cytotoxic chemotherapy. In a well-established, erlotinib-resistant, T790M-positive NSCLC murine model, adding G1T38 to erlotinib treatment resulted in a 77% delay in tumor growth compared with erlotinib alone; whereas, erlotinib alone showed no statistically significant change compared with vehicle control. Furthermore, the addition of G1T38 to afatinib treatment nearly doubled the time to resistance when compared with treatment with afatinib only. Finally, in murine tumors that became resistant to afatinib, the addition of G1T38 caused stable disease (SD). These results suggest that the addition of G1T38 to an EGFR inhibitor could potentially extend PFS in patients with NSCLC.
Clinical Phase	1b/2
Indication	Treatment of EGFR T790M mutation-positive metastatic (Stage IV) NSCLC after first-line EGFR TKI failure

Objectives

	Part 1 (Phase 1b)	Part 2 (Phase 2)
Primary Objectives		
Evaluate DLTs associated with G1T38 administered with osimertinib	X	
Determine the recommended Phase 2 dose of G1T38 administered with osimertinib	X	
Evaluate the safety and tolerability of G1T38 administered with osimertinib	X	X
Assess PFS using BICR (RECIST v1.1)		X
Secondary Objectives		
Assess the effect of osimertinib on PK parameters of G1T38	X	
Assess PFS using investigator assessments (RECIST v1.1)	X	X
Assess response rate and CBR based on RECIST v1.1 (BICR and investigator assessed)	X	X
Assess OS	X	X
Assess 1-year PFS (BICR and investigator assessed)	X	X
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]

CBR = clinical benefit rate; cfDNA = cell-free deoxyribonucleic acid; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; BICR = blinded independent central review

Study Design	This is a Phase 1b/2, multicenter, open-label study of the safety, tolerability, pharmacokinetics (PK), and efficacy of G1T38 in combination with osimertinib for patients with EGFR mutation-positive metastatic NSCLC. This open-label study consists of 2 parts: Part 1 will evaluate the effect of osimertinib on the PK parameters of G1T38 and the safety and tolerability (including dose-limiting toxicities [DLTs]) of escalating doses of G1T38 in combination with osimertinib to determine the recommended Phase 2 dose (RP2D); and Part 2 will be a randomized portion to further evaluate the safety, tolerability, and efficacy of the RP2D. Both parts of the study include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of the first dose of study drug and completes at the Post-Treatment visit. **Part 1** *Part 1 Pharmacokinetic Interaction and Dose-Escalation Cohorts* *Cohort 1:* Six patients will be enrolled in the first cohort in Part 1 to assess the potential effect of osimertinib on the PK parameters of G1T38. G1T38 is a substrate of the breast cancer resistance protein (BCRP) transporter protein and osimertinib has been shown to increase the area under the concentration-time curve (AUC) and maximum concentration (C_{max}) of concurrently administered rosuvastatin, a BCRP substrate, by 35% and 72%, respectively. Patients will receive a single oral dose of G1T38 200 mg on Cycle 1 Day -16 and blood samples for G1T38 PK evaluation will be collected over the subsequent 48-hour period. Patients will then receive oral osimertinib 80 mg once daily without G1T38 on Cycle 1 Days -14 to -3, and then both G1T38 and osimertinib on Cycle 1 Day -2, after which blood samples for G1T38 PK evaluation will be collected over the subsequent 48-hour period. Osimertinib once-daily dosing will continue on Cycle 1 Day -1 and through the end of the Treatment Phase. On Cycle 1 Day 1, patients will begin G1T38 once-daily dosing, which will continue through the end of the Treatment Phase (note: there is no Day 0 in the study). DLTs will be evaluated from Cycle 1 Day -16 through Cycle 1 Day 28 (the DLT period). A safety monitoring committee (SMC) will evaluate all safety and available PK data through the DLT period for Cohort 1 prior to the enrollment of additional cohorts. *Cohorts 2 and beyond:* Following completion of Cohort 1, additional sequential dose-escalation cohorts may be enrolled using a standard 3 + 3 design and will follow the same schedule as described for the first cohort. All dose escalation/de-escalation recommendations made by the SMC will be based on review of safety and available PK data from the DLT period of the current cohort, as well as the cumulative safety data from all patients enrolled. *Definition of Dose-Limiting Toxicities* Dose-limiting toxicities are drug-related adverse events (AEs) defined as follows: • Grade 4 neutropenia • ≥ Grade 3 neutropenic infection/febrile neutropenia • Grade 4 thrombocytopenia

	• ≥ Grade 3 thrombocytopenia with bleeding • ≥ Grade 3 nonhematologic toxicity (additional criterion for nausea, vomiting, diarrhea, or fatigue: lasting > 5 days with maximal medical management) • Liver function test abnormalities meeting Hy's Law criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 3 × upper limit of normal [ULN] and total bilirubin ≥ 2 × ULN). All study drugs must be permanently discontinued in any patient meeting Hy's Law criteria. **Part 2** In Part 2, eligible patients will be enrolled into a randomized portion of the study. Patients will be randomized (1:1) to receive osimertinib or G1T38 (at the RP2D) + osimertinib, with stratification by presence of central nervous system (CNS) metastases (yes versus no) and ethnicity (Asian versus non-Asian). Following screening, patients will begin osimertinib or G1T38 + osimertinib once-daily oral dosing on Cycle 1 Day 1. Patients who are initially randomized to receive osimertinib alone may crossover to the G1T38 + osimertinib group at the time of disease progression as determined by blinded independent central review (BICR). An independent data monitoring committee (IDMC) shall review all cumulative safety and efficacy data, as well as all available PK data, approximately every 4 months during the Treatment Phase.
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. Patients in Part 2 who are initially randomized to receive osimertinib alone may crossover to the osimertinib + G1T38 arm at the time of disease progression.
Study Duration	Part 1: The duration of Part 1 will be approximately 9 months. Part 2: The ORR is expected to read out approximately 1 year after Part 2 enrollment begins. PFS is expected to read out approximately 2.5 years after Part 2 enrollment begins. The Survival Follow-up Phase will continue until at least 50% of the patients in Part 2 have died.
Approximate Number of Patients	Overall, up to 144 patients will be enrolled in the study. In Part 1, up to 36 patients may be enrolled. In Part 2, 108 patients will be enrolled.
Number of Study Centers	Approximately 50 centers globally may participate.
Diagnosis and Key Criteria for Inclusion	For a patient to be eligible for participation in this study, all of the following criteria must apply. A full list of inclusion criteria are provided in Section 7.1.1. • Women or men, 18 years or older • Histologic or cytologic confirmed diagnosis of NSCLC • Stage IV NSCLC

	• Documented EGFR mutation (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q) o *Part 2 Only:* Tumor T790M mutation-positive status based on an appropriate test (tumor biopsy or cell-free DNA [cfDNA]) taken after documented disease progression on first-line treatment with a first or second generation EGFR TKI • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks • Evaluable (Part 1 only) or measurable disease • Left ventricular ejection fraction (LVEF) ≥ institution's lower limit of the reference range • Adequate bone marrow reserve and organ function as demonstrated by the following laboratory values: o Hemoglobin ≥ 90 g/L o ANC ≥ 1.5×10^9/L o Platelet count ≥ 100×10^9/L o Calculated creatinine clearance ≥ 50 mL/minute o Total bilirubin ≤ 1.5 × ULN; < 3 × ULN if the patient has documented Gilbert's disease or liver metastases o ALT < 2.5 × ULN if no demonstrable liver metastases or < 5 × ULN in the presence of liver metastases o AST < 2.5 × ULN if no demonstrable liver metastases or < 5 × ULN in the presence of liver metastases *Additional criteria that apply to Part 2 only*: • Measurable disease as defined in RECIST, Version 1.1, as determined by the investigator
Key Criteria for Exclusion	A patient will not be eligible for participation in this study if any of the following criteria apply. A full list of exclusion criteria are provided in Section 7.1.2. o Treatment with any of the following: o EGFR TKIs (erlotinib, gefitinib, afatinib, osimertinib) within 9 days of the first dose of study drug; other approved EGFR TKIs within 5 half-lives of the first dose of study drug o Investigational agents within 28 days, or 5 half-lives, whichever is longer, of the first dose of study drug; antibody based therapy within 6 weeks of the first dose of study drug o *Part 1 only*: More than 2 prior lines of cytotoxic chemotherapy for advanced NSCLC o *Part 2 only*: Any prior cytotoxic chemotherapy for advanced NSCLC ▪ *Part 2 only*: Previous treatment with osimertinib or other T790M active EGFR TKI o Blood transfusions or hematopoietic growth factor therapy within 14 days of first screening visit o Prior radiotherapy treatment to > 25% of the bone marrow or radiotherapy with a wide field of radiation within 28 days of the

	first dose of study drug ○ Patients receiving medications, herbal supplements, or foods known to be potent inhibitors of cytochrome P450 (CYP)3A4 or orally administered sensitive substrates of CYP3A4 within 14 days prior to first dose of study drug (see Sections 8.5.1 and 8.5.2) ○ Patients receiving medications, herbal supplements, or foods known to be potent inducers of CYP3A4 within 21 days prior to first dose of study drug (see Section 8.5.2) ○ Patients receiving medications, herbal supplements, or foods known to be potent inhibitors of BCRP within 14 days prior to first dose of study drug (see Section 8.5.2) ○ *Part 1 only:* Patients receiving medications that raise gastric pH within 7 days prior to first dose of study drug (see Section 8.5.5). ○ Any unresolved toxicities from prior surgeries or therapy > Grade 1 (Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) at the time of starting study drug with the exception of alopecia (any grade) and platinum therapy-related peripheral neuropathy (> Grade 2) ○ Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they are currently asymptomatic and clinically stable off anticonvulsants and steroids for at least 28 days prior to first dose of G1T38. ○ Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol ○ Known chronic, active infection ○ Cardiac criteria as outlined in Section 7.1.2 ○ Past medical history of interstitial lung disease, drug-induced interstitial lung disease (ILD), radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease ○ Prior hematopoietic stem cell or bone marrow transplantation
Other Medicinal Products	Osimertinib 80 mg orally once daily, with or without food.
Investigational Medicinal Product Dosage and Administration	G1T38 will be administered orally once daily. The starting dose for Part 1 will be a G1T38 dose of 200 mg once daily and subsequent dose levels will be determined by the SMC. All patients in Part 2, will receive the RP2D selected by the SMC. All doses of G1T38 shall be administered with food.

Efficacy Evaluation	Efficacy will be assessed by evaluation of tumor response based on RECIST, Version 1.1, including objective response rate (ORR), clinical benefit rate (CBR), PFS, and overall survival (OS). Parts 1 and 2 will utilize investigator assessments and Part 2 will also utilize assessments from BICR.
Safety Evaluation	Safety will be assessed by evaluation of AEs, physical examinations, vital signs measurements, clinical laboratory data, echocardiograms/ multigated acquisition (MUGA) scans, ophthalmic examinations, and electrocardiograms (ECGs).
Pharmacokinetics Evaluation	In Part 1, serial blood samples will be collected at specified time points from all patients for the measurement of plasma concentrations of G1T38 [redacted]. Pharmacokinetic parameters will be derived from G1T38 [redacted] plasma concentration-time data. Osimertinib trough concentrations will also be evaluated to confirm compliance. In Part 2, a limited number of blood samples shall be collected for population PK analysis of G1T38 [redacted].
Cell-Free DNA Evaluation	Changes in mutational status at selected time points will be assessed and correlated with clinical outcomes.
Statistical Analysis	Data will be summarized separately by study part (Part 1 and Part 2). Data from Part 1 will be summarized descriptively by dose level, if applicable, and overall. Selected safety summaries will include combined data from both Parts 1 and 2 of the study. The descriptive summary for the categorical variables will include counts and percentages. The ORRs and their corresponding 95% exact confidence intervals (CIs) will be calculated by Clopper-Pearson method. The descriptive summary for the continuous variables will include mean, median, standard deviation (StD), and minimum and maximum. The descriptive summaries of time-to-event data will include median, 25% and 75% percentiles, and standard error. The Kaplan-Meier method will also be used to summarize the time-to-event data. All CIs will be 95%, unless stated otherwise. All data will be listed for all patients. For Part 2 of the study, patients will be randomized (1:1) to receive osimertinib or G1T38 + osimertinib. The randomization will be stratified based on presence of CNS metastases (yes versus no) and ethnicity (Asian versus non-Asian). PFS assessed by BICR according to RECIST v1.1 is the primary endpoint for Part 2 of the study. The 1-sided stratified log-rank test will be used to compare the 2 treatment groups. A Cox regression analysis with a fixed effect for treatment arm and stratification factors will be used to estimate the hazard ratio (HR) and its 80% CI. OS will be analyzed in a similar way. Overall tumor response endpoints such as ORR and CBR are secondary endpoints for Part 2 of the study. A 1-sided stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare the

	2 treatment groups. The odds ratio and its associated 80% CI will be presented. In addition, potential influences of baseline patient characteristics such as age, ECOG performance status, and selected biomarkers on the endpoints may be evaluated to compare the 2 treatment groups. For Part 2 of the study, because crossover to G1T38 + osimertinib is allowed for patients following progression on osimertinib alone, the treatment effect on OS may be confounded and may not be estimated properly by the above defined methods. Therefore, an exploratory analysis will be performed using the rank-preserving structural failure time (RPSFT) method and Cox model with inverse probability of censoring weighting (IPCW) to correct for confounding introduced by the crossover. *Safety Analysis* The safety analysis will include all treated patients. Descriptive statistics of safety will be presented. All treatment-emergent AEs, drug-related AEs, serious adverse events (SAEs), and drug-related SAEs will be tabulated using worst grade per National Cancer Institute (NCI) CTCAE, Version 4.03 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, and liver function tests will also be summarized using worst grade per NCI CTCAE, Version 4.03 criteria.
Rationale for Number of Patients	It is estimated that up to 36 patients will be enrolled in the dose-escalation part of the study (Part 1). The actual number of patients will depend on the number of dose levels/cohorts that are tested. For the randomized part of the study (Part 2), it is assumed that the overall 1-sided type I error rate is 0.1 and the type II error rate used to compute sample size is 0.20 (corresponding to 80% power). Patients will be randomized using a 1:1 treatment allocation ratio between the 2 treatment groups (osimertinib versus G1T38 + osimertinib). Assuming a 10.1 month median PFS for the osimertinib group based on historical data, and an HR of 0.6, the required number of PFS events is 70. Assuming an accrual period of 12 months and an additional follow-up period of 18 months after the last patient is enrolled, the calculated total sample size is 98 patients. Allowing for a dropout/lost-to-follow-up rate of approximately 10%, gives an adjusted total sample size of 108 patients for Part 2.

4. INTRODUCTION

4.1. Background

The cyclin D/cyclin-dependent kinase 4/6 (CDK4/6)/p16^{INK4a}/retinoblastoma protein (Rb) pathway is frequently disrupted in cancer. A majority of human neoplasms maintain functional Rb, but have aberrations that increase the activity of CDK4/6, which inhibits Rb function and allows cell proliferation (Ortega et al 2002; Shapiro 2006). As such, CDK4/6 appears to be a key enzyme necessary for the proliferation of human cancers that have functional Rb. G1 Therapeutics, Inc. is developing G1T38 as a potent and selective small molecule inhibitor of the CDK4/6-cyclin D complex for oral treatment of patients with CDK4/6-dependent tumors, such as non-small cell lung cancer (NSCLC).

NSCLC represent the vast majority of lung cancers around the world, and epidermal growth factor receptor (EGFR) mutations occur in approximately 15% of NSCLC in the United States and up to 62% of cases in Asia. Osimertinib (Tagrisso®), a third generation EGFR tyrosine kinase inhibitor (TKI), has been established as the second-line standard of care in patients with metastatic EGFR T790M mutation positive NSCLC whose disease has progressed on or after a first-line EGFR TKI, and has also recently demonstrated benefit in first-line EGFR-positive NSCLC regardless of T790M status (Sequist and Neal, 2017; Ramalingam et al 2017). Standard of care treatment following disease progression with osimertinib remains parenteral cytotoxic chemotherapy as no oral treatment options currently exist in this setting.

Historical median progression-free survival (PFS) with osimertinib monotherapy is approximately 10 months, and the overall response rate (ORR) is approximately 70% (Tagrisso Prescribing Information 2017). Nearly all patients eventually develop resistance to osimertinib and experience disease progression. The putative resistance mechanisms to osimertinib include activating mutations in PIK3CA, MEK1, and KRAS, and/or amplifications in MET, human epidermal growth factor receptor 2 (HER2), fibroblast growth factor receptor 1 (FGFR1), and activation of the insulin-like growth factor 1 receptor (IGF1R) pathway; many of these are upstream of CDK4/6 (Ramalingam et al 2017; Minari et al 2016; Ko et al 2017). G1T38 has the potential to block these resistance pathways, delay the time to resistance, and prolong PFS when added to osimertinib, and thus has the potential to delay the need for cytotoxic chemotherapy. Nonclinical osimertinib-resistant tumor models are not currently available. Therefore, the addition of G1T38 to either erlotinib or afatinib, which are first and second generation EGFR inhibitors, respectively, has been evaluated in the H1975 mouse model (EGFR$^{L858R/T790M}$) to assess proof of principle. Tumor growth delay was compared in mice treated with an EGFR inhibitor (erlotinib or afatinib) alone or EGFR inhibitor and G1T38. As the EGFR^{T790M} mutation is known to accelerate time to resistance to afatinib and erlotinib, it was anticipated that erlotinib alone would be ineffective and the time to afatinib resistance would be short. As expected, mice treated with erlotinib showed no statistically significant difference in tumor growth when compared to the vehicle only cohort. However, when G1T38 was added to erlotinib treatment, there was a 77% tumor growth delay when compared to controls, suggesting the addition of G1T38 reversed erlotinib resistance. Furthermore, the addition of G1T38 to afatinib treatment extended time to resistance from 18 days (afatinib alone) to

34 days (afatinib + G1T38). Lastly, in tumors that had progressed on afatinib alone, the addition of G1T38 resulted in stabilization of tumor growth (SD). These data provide strong nonclinical rationale for the addition of G1T38 to an EGFR TKI in patients, and are likely to extend to osimertinib in the EGFR T790M mutation setting.

The addition of G1T38 to osimertinib follows the general paradigm of adding a CDK4/6 inhibitor to targeted therapies, which has been shown to extend PFS in estrogen receptor-positive (ER+) breast cancer. In the PALOMA-3 study, addition of palbociclib (a CDK4/6 inhibitor) to fulvestrant (a selective estrogen receptor degrader) extended median PFS from 4.6 months (fulvestrant alone) to 9.5 months (palbociclib + fulvestrant) (Cristofanilli et al 2016). Similar significant gains in PFS have been observed with ribociclib, another CDK4/6 inhibitor (Hortobagyi et al 2016).

The safety profile of G1T38 (in the ongoing Phase 1/2 study; NCT02983071) is similar to other CDK4/6 inhibitors such as palbociclib, with neutropenia being the most common drug-related adverse event (AE) and with Grade 1 and 2 gastrointestinal effects (nausea, vomiting, and diarrhea) also being observed.

Based on the nonclinical data and the preliminary human safety data, the addition of G1T38 to osimertinib warrants clinical study and has the potential to offer clinical benefit in patients that have failed first-line EGFR inhibitors.

[redacted]

4.2.4. Potential Risks

Based upon nonclinical safety studies at exposures that were at or above the expected exposure in humans, potential adverse effects with G1T38 administration are presented below by body system:

- *Blood and lymphatic system disorders*: anemia, bone marrow hypocellularity, leukopenia, neutropenia (afebrile or febrile), monocytopenia, lymphopenia, and/or thrombocytopenia
- *Infections and infestations*: viral and/or bacterial, with the potential to develop sepsis
- *Injury and procedural complications:* bruising

Palbociclib (IBRANCE®), ribociclib (KISQALI®), and abemaciclib (Verzenio®) are selective CDK4/6 inhibitors for the treatment of hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with endocrine therapy that have been approved by the United States (US) Food and Drug Administration (FDA). Given the similar mechanism of action to G1T38, the AE profile of G1T38 may be similar to that observed with these 3 compounds. In general, the most common adverse reactions with CDK4/6 inhibitors (incidence ≥ 10%) are neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, constipation, headache, back pain, and pyrexia (Palbociclib Prescribing Information 2017; Ribociclib Prescribing Information 2017, Abemaciclib Prescribing Information 2017).

4.3. Summary of Clinical Data

A first-in-human (FIH), single-dose, placebo-controlled, Phase 1 study (G1T38-01) of G1T38 in healthy male and female subjects has been completed. A total of 75 subjects were dosed in this study and 57 subjects were exposed to oral doses of G1T38. Dosing started at 3 mg G1T38 and the highest dose administered was 600 mg. The 600 mg total dose was explored as a single dose as well as two 300 mg doses separated by 12 hours. A Food Effect Cohort assessing the effect of a high-fat meal on a single 300 mg dose has also been completed. Safety data as of 25 August 2017 from an ongoing Phase 1/2 study of G1T38 + fulvestrant in patients with advanced HR-positive breast cancer (Study G1T38-02; NCT02983071) is also summarized below.

4.3.1. Clinical Safety and Tolerability

Potentially G1T38 treatment-related AEs are summarized herein. For further information, please refer to the G1T38 IB.

In Study G1T38-01, single or twice daily (total daily dose split into 2 equal doses, taken every 12 hours) oral doses of G1T38 in the dose range of 3 to 600 mg/day appeared to be well to moderately tolerated in a group of healthy male and female subjects. In most subjects with moderate tolerability, gastrointestinal AEs were the most common moderate intensity treatment-emergent AEs (TEAEs). Dosing under fed conditions appeared to improve gastrointestinal tolerability. Effects on hematologic parameters were not observed due to the limited duration of dosing.

There were no deaths, other serious adverse events (SAEs), or AEs that led to withdrawal from the study and no subjects experienced severe or life-threatening TEAEs. For subjects treated with G1T38 in Study G1T38-01, 37 (65%) subjects reported a total of 121 treatment-related TEAEs. The most frequently (≥ 20% of subjects) reported treatment-related TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) were gastrointestinal disorders (reported by 60% of pooled G1T38-dosed subjects versus 17% of pooled placebo-dosed subjects) and nervous system disorders (33% for both pooled G1T38-dosed subjects and placebo-dosed subjects). The most frequently (≥ 10% of all subjects) reported treatment-related TEAEs by preferred term were diarrhea (reported by 46% of pooled G1T38-dosed subjects versus 6% of pooled placebo-dosed subjects), nausea (33% versus 6%, respectively), headache (18% versus 22%, respectively), and fatigue (12% versus 6%, respectively). Note: Six subjects reported ‘loose stool(s)’ that did not meet the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 definition of diarrhea that requires an increase in stool frequency; however, the MedDRA codes ‘loose stool(s)’ to diarrhea. Exclusion of these 6 subjects with loose stool(s), resulted in 20 out of 57 (35%) of pooled G1T38-dosed subjects reporting diarrhea. The intensity of loose stool(s) in all 6 subjects was reported as mild.

Sixteen (28%) of 57 G1T38-dosed subjects experienced at least 1 treatment-related TEAE of moderate (Grade 2) intensity. The most common treatment-related TEAEs of moderate intensity were diarrhea in 6 (11%) subjects, nausea in 5 (9%) subjects, headache in 5 (9%) subjects, and somnolence in 2 (4%) subjects. In the placebo group, 1 treatment-related headache of moderate severity was reported in 1 (6%) placebo-dosed subject.

Gastrointestinal tolerability of G1T38 was improved by dosing concurrently with a high-fat meal. Four (50%) of 8 subjects in the fed state versus 8 (100%) of 8 subjects in the fasted state experienced a gastrointestinal TEAE.

In ongoing Study G1T38-02, as of the data cut date of 25 August 2017, 18 patients have received at least 1 dose of G1T38. Dose levels administered included 200 mg once daily (n = 6); 100 mg twice daily (n = 6); 300 mg once daily (n = 3); and 150 mg twice daily (n = 3). G1T38 is administered on a continuous daily dosing schedule and the longest duration of therapy was 197 days as of 25 August 2017. One DLT of Grade 4 neutropenia has been observed in 1 patient administered 200 mg G1T38 once daily. This patient’s neutropenia recovered with dose interruption for 20 days and treatment was restarted at 150 mg once daily with no further episodes of Grade 4 neutropenia. No deaths or SAEs have been reported to date.

Fifteen of 18 patients (83.3%) had at least 1 G1T38-related AE (Table 4-1). The most common G1T38-related AEs occurring in ≥ 5 subjects were neutrophil count decreased (9 subjects [50%]), white cell count decreased (7 subjects [38.9%]), anemia (6 subjects

[33.3%]), neutropenia (5 subjects [27.8%]), diarrhea (5 subjects [27.8%]), and nausea (5 subjects [27.8%]).

Table 4-1 Summary of G1T38-Related Adverse Events by Preferred Term and CTCAE Grade Occurring in Study G1T38-02 (as of 25 August 2017)

	G1T38-02 (N = 18)[a]				
Preferred Term	**Grade 1-2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Overall n (%)**
Number (%) of patients with any G1T38-related TEAEs	11 (61.1)	3 (16.7)	1 (5.6)	0	15 (83.3)
Neutrophil count decreased	7 (38.9)	2 (11.1)	0	0	9 (50.0)
White blood cell count decreased	7 (38.9)	0	0	0	7 (38.9)
Anaemia	6 (33.3)	0	0	0	6 (33.3)
Diarrhoea	5 (27.8)	0	0	0	5 (27.8)
Nausea	5 (27.8)	0	0	0	5 (27.8)
Neutropenia	3 (16.7)	1 (5.6)	1 (5.6)	0	5 (27.8)
Haematuria	3 (16.7)	0	0	0	3 (16.7)
Vomiting	3 (16.7)	0	0	0	3 (16.7)
Blood creatinine increased	2 (11.1)	0	0	0	2 (11.1)
Platelet count decreased	2 (11.1)	0	0	0	2 (11.1)
Alopecia	1 (5.6)	0	0	0	1 (5.6)
Blood bilirubin increased	1 (5.6)	0	0	0	1 (5.6)
Blood lactate dehydrogenase increased	1 (5.6)	0	0	0	1 (5.6)
Blood urea increased	1 (5.6)	0	0	0	1 (5.6)
Dry eye	1 (5.6)	0	0	0	1 (5.6)
Dry mouth	1 (5.6)	0	0	0	1 (5.6)
Lacrimation increased	1 (5.6)	0	0	0	1 (5.6)
Leukopenia	1 (5.6)	0	0	0	1 (5.6)
Monocyte count decreased	1 (5.6)	0	0	0	1 (5.6)
Stomatitis	1 (5.6)	0	0	0	1 (5.6)

Preferred Term	G1T38-02 (N = 18)[a]				
	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Overall n (%)
Thrombocytopenia	1 (5.6)	0	0	0	1 (5.6)
Vertigo	1 (5.6)	0	0	0	1 (5.6)

AE = adverse event; CTCAE = Common terminology criteria for adverse events; TEAE = treatment-emergent adverse event

AEs that started on or after the day of the first dose of study drug were included. AEs with an unknown/not reported onset date were also included. AEs considered by the investigator to be possibly, probably, or definitely related were classified as G1T38-related. Patients with multiple events in the same category were counted only once in that category, at the maximum observed CTCAE grade. Patients with events in more than 1 category were counted once in each of those categories. Number (%) of patients with AEs, sorted by preferred term in decreasing order of frequency (by overall). If the frequencies tied, an alphabetic order was applied. Cumulative data available up to 25 August 2017 was included.

a N is the number of patients who received at least 1 dose of G1T38, and is the denominator of percentages.

4.3.2. Clinical Pharmacokinetics

4.3.2.1. Pharmacokinetics in Healthy Volunteers: Study G1T38-01

Single-Dose Capsules

Following oral dosing in the fasted state, for the 48 mg dose level and beyond, G1T38 concentrations in plasma were quantifiable from the first (0.25 hour) or second (0.5 hour) postdose time point, with median time to peak concentration (T_{max}) increasing with increasing dose, from 2 hours up to 6 hours postdose. After reaching peak concentrations, a multiphasic decline in plasma concentrations was observed. The geometric mean terminal phase elimination half-life ($t_{1/2}$) for G1T38 was between 13.8 and 17.2 hours.

Effect of Food

Median T_{max} was 6 hours postdose following a dose of 300 mg both under fasting or fed conditions. The geometric mean C_{max} was slightly higher following dosing in the fed (high-fat meal) versus fasting state. Exploratory statistical analysis indicated a very small food effect (13%) on C_{max} and no food effect on area under the concentration-time curve $(AUC)_{0-t}$ and $AUC_{0-\infty}$.

Dose Proportionality

Based on the dose-normalized PK parameter plots, both C_{max} and AUCs increased with dose in a more than dose-proportional manner at the lower doses (48 to 200 mg G1T38), and in an approximately dose-proportional (AUCs) or less than dose-proportional (C_{max}) manner over the dose range of 200 to 400 mg G1T38.

[redacted]

4.3.2.2. Pharmacokinetics in Patients with Cancer: Study G1T38-02

Dosing Regimens

Patients in Part 1 of Study G1T38-02 were dosed with orally administered G1T38 either once or twice daily on a continuous basis. Pharmacokinetic data are available for the 200 mg (starting dose for once-daily dosing) and 300 mg once-daily cohorts; and for the 100 mg (starting dose for twice-daily dosing) and 150 mg twice-daily cohorts. The patients were instructed to take all doses with food.

Pharmacokinetic Results

The preliminary PK results suggested that the PK profile for G1T38 in patients is similar to the profile observed in healthy volunteers. T_{max} was typically observed 2 to 4 hours after dosing for all dosing regimens. C_{max} and AUC values tended to increase slightly greater than proportional to the dose in the once-daily cohorts. There was minimal accumulation between the first dose on Week 1 and the steady state dose at Week 5. G1T38 C_{max} and AUC_{τ} values also increased greater than proportional to the dose during twice-daily dosing at dose levels of 100 and 150 mg twice daily. Due to the delayed T_{max} and the 12- or 24-hour dosing intervals, it was not possible to estimate the terminal phase half-life of G1T38 in Study G1T38-02.

[redacted]

4.4. Study and Dose Rationale

4.4.1. Study Rationale

Osimertinib has become standard of care therapy for patients with NSCLC that have experienced disease progression on first-line EGFR inhibitors and harbor the EGFR T790M mutation. Historical median PFS with second-line osimertinib monotherapy is approximately 10 months, and the ORR is approximately 70% (Tagrisso Prescribing Information 2017). While osimertinib is effective in most patients, nearly all patients will eventually develop resistance to osimertinib and subsequent disease progression. The addition of an oral CDK4/6 inhibitor such as G1T38 to osimertinib has the potential to prolong the PFS time by interfering with the typical resistance mechanisms that develop to osimertinib.

Potential Drug-Drug-Interaction

Osimertinib has been evaluated in several drug-drug interaction (DDI) studies in humans. Based on the results of these studies, only 1 potential, clinically relevant DDI between osimertinib and G1T38 has been identified (Tagrisso Prescribing Information 2017). Osimertinib is an inhibitor of the BCRP efflux transporter and G1T38 is a substrate of BCRP. BCRP is located in the gut wall where it actively limits the absorption of substrate molecules (ie, substrates are effluxed into the gut lumen rather than absorbed into the systemic circulation). Osimertinib has been shown to increase the AUC and C_{max} of concurrently administered rosuvastatin, a BCRP substrate, by 35% and 72%, respectively. Part 1 of this study will assess the extent of this potential DDI.

Based on the DDI information available for osimertinib and the nonclinical evaluation of G1T38, it is highly unlikely that G1T38 will alter the PK of osimertinib. This conclusion is based on the mitigating data in Table 4-2.

Table 4-2 Osimertinib and G1T38: Potential Risks for Drug-Drug Interactions and Mitigating Data

Potential Risk	Mitigating Data
G1T38 inhibits CYP3A4 (IC_{50} = 78 µM) and osimertinib is CYP3A4 substrate	The strong CYP3A4 inhibitor itraconazole had no clinically meaningful effect on the PK of osimertinib
Osimertinib is a CYP3A4 substrate	G1T38 does not induce CYP3A4
G1T38 inhibits BCRP (IC_{50} = 7.21 µM) and osimertinib is a BCRP substrate	Does not meet FDA threshold[a] as clinically relevant using the following FDA formula: $[I]/IC_{50} \geq 0.1$, where [I] represents the mean anticipated steady-state G1T38 total C_{max} for a 600 mg G1T38 dose (0.338 µM) $[I]/IC_{50}$ = 0.338 µM/7.21 µM = 0.0468

a *FDA Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.*

4.4.2. Dose Rationale

Part 1

Single doses of up to 600 mg of G1T38 were safely administered in the FIH study [redacted] with no ≥ Grade 3 study G1T38-related AEs observed. The ongoing Phase 1/2 patient study (G1T38-02) utilizing continuous daily doses of G1T38 in combination with fulvestrant has examined G1T38 doses of 200 mg once daily, 300 mg once daily, 400 mg once daily, 100 mg twice daily, and 150 mg twice daily with no observed SAEs to date and only one G1T38-related DLT of Grade 4 neutropenia in a patient receiving 200 mg once daily, who had a baseline absolute neutrophil count (ANC) of 1500 cells/mL. The neutropenia recovered following a 20-day interruption of G1T38 dosing and re-initiation of G1T38 at 150 mg once daily thereafter. The patient remains on study at this reduced dose for > 100 days without the occurrence of Grade 4 neutropenia. Subsequent to the G1T38-02 data cut date of 25 August 2017, the 400 mg once-daily dose has been determined to be tolerable (no DLTs in the 3 patient cohort) by the safety monitoring committee (SMC) and the study is currently enrolling patients at a G1T38 dose of 500 mg once daily.

Osimertinib is classified as a weak inhibitor of BCRP according to the *FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (2012)*. AUC is considered the most relevant parameter in terms of G1T38 safety as the chronic administration of CDK4/6 inhibitors such as G1T38 appears to be the primary factor leading to clinically significant neutropenia, whereas brief relatively higher concentrations (ie, C_{max}) appear to have little effect on neutropenia as was observed in Study G1T38-01.

The starting dose of G1T38 will be 200 mg once daily in combination with 80 mg once daily osimertinib. This G1T38 dose allows a safety coverage of 100% relative to the G1T38 dose of 400 mg once daily that was well tolerated in the ongoing Phase 1b/2 study (dose escalation

ongoing; dose level as of 04 October 2017 was 500 mg once daily). It is anticipated that the potential effect of osimertinib on the PK parameters of G1T38 will not exceed that observed with rosuvastatin (a model BCRP substrate).

Following assessment of the safety, tolerability and PK data for the first cohort in this study, subsequent cohorts will be enrolled utilizing a 3+3 design as described in Section 6.1.1.

Part 2

The doses of G1T38 and osimertinib to be used in Part 2 of the study will be determined during Part 1 as described in Section 6.1.1.

4.5. Risk/Benefit Assessment

The safety profile of G1T38 observed to date in the ongoing Phase 1/2 study is similar to other CDK4/6 inhibitors such as palbociclib, with neutropenia being the most common drug-related AE and with Grade 1 and 2 gastrointestinal effects (nausea, vomiting, and diarrhea) also being observed. There have been no observed G1T38-related pulmonary, cardiac, skin, or clinically significant ophthalmic AEs to date (see Section 4.3.1).

The most common osimertinib-related AEs (≥ 20%) are diarrhea (41%), rash (34%), dry skin (23%), nail toxicity (22%), and fatigue (22%) (Tagrisso Prescribing Information 2017). Significantly less frequent, but potentially more severe osimertinib-related AEs include pneumonitis/interstitial lung disease, QTc prolongation, cardiomyopathy, and keratitis. Based on extensive nonclinical data and clinical data to date with G1T38, none of these more severe osimertinib-related AEs have been observed with G1T38 to date. This study includes appropriate exclusion criteria, baseline examinations, and on-study monitoring to carefully exclude at-risk patients and to evaluate patients for the development of these more severe osimertinib-related AEs during the course of the study. Management of osimertinib related toxicities shall follow the prescribing information for osimertinib (Tagrisso Prescribing Information 2017; see Appendix 2).

Neutropenia, the vast majority Grade 1 or 2, has also been observed with osimertinib therapy, with up to 2.2% of patients experiencing Grade 3 neutropenia. Absolute neutrophil counts will be monitored weekly for the first 8 weeks (2 cycles) then every other week for the next 2 cycles. Beginning with Cycle 5 Day 1, patients with stable ≤ Grade 2 hematologic parameters may have hematology monitored monthly (Day 1 of each cycle); patients that do not meet this criteria will continue to have every other week assessment of hematologic parameters. The neutropenia induced by CDK4/6 inhibitors, including G1T38, is reversible with interruption of therapy and dose reduction if necessary. Specific guidelines for managing neutropenia are included in Section 8.3.3.

Patients will be carefully monitored for potential gastrointestinal AEs and managed symptomatically with appropriate therapies. G1T38 will also be dosed with food as this was shown to improve gastrointestinal tolerability in the FIH study.

In summary, the potential benefits of extending PFS with osimertinib plus G1T38 and delaying the need for cytotoxic chemotherapy outweigh the potential risks of gastrointestinal AEs and neutropenia, both of which are easily monitored and treatable. Furthermore, febrile

neutropenia with the CDK4/6 inhibitor palbociclib in combination with fulvestrant has been reported in only 0.9% of patients, indicating a low risk to the patient, and neutropenia in general with CDK4/6 inhibitors recovers in the vast majority of patients with treatment interruption and/or dose reduction (Palbociclib Prescribing Information 2017).

5. STUDY OBJECTIVES

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

Table 5-1 Study Objectives

	Part 1 (Phase 1b)	Part 2 (Phase 2)
Primary Objectives		
Evaluate DLTs associated with G1T38 administered with osimertinib	X	
Determine the recommended Phase 2 dose of G1T38 administered with osimertinib	X	
Evaluate the safety and tolerability of G1T38 administered with osimertinib	X	X
Assess PFS using BICR (RECIST v1.1)		X
Secondary Objectives		
Assess the effect of osimertinib on PK parameters of G1T38	X	
Assess PFS using investigator assessments (RECIST v1.1)	X	X
Assess response rate and CBR based on RECIST v1.1 (BICR and investigator assessed)	X	X
Assess OS	X	X
Assess 1-year PFS (BICR and investigator assessed)	X	X
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]

CBR = clinical benefit rate; cfDNA = cell-free deoxyribonucleic acid; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; BICR = blinded independent central review

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This open-label study consists of 2 parts: Part 1 will evaluate the effect of osimertinib on the PK parameters of G1T38 and the safety and tolerability of escalating doses of G1T38 in combination with osimertinib to determine the recommended Phase 2 dose (RP2D); and Part 2 will be a randomized portion to further evaluate the safety, tolerability, and efficacy of the RP2D. Both parts of the study include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of the first dose of study drug and completes at the Post-Treatment Visit.

6.1.1. Part 1

The goals of Part 1 are to determine the effect of osimertinib on the PK parameters of G1T38 and to determine the RP2D of G1T38 in combination with osimertinib by assessing the safety (including DLTs), tolerability, PK, and efficacy of escalating doses of G1T38 administered with osimertinib.

During Part 1, an SMC will provide oversight and guidance regarding safety concerns, as outlined in the SMC Charter. All dose escalation/de-escalation decisions will made by the SMC, which will be comprised of the sponsor, medical monitor, independent medical doctor, and the principal investigator(s). The SMC will make the final dose determination for each subsequent cohort. Therefore the actual dose may differ from the projected dose levels in Table 6-1 as the SMC may determine that intermediate dose levels warrant exploration.

Part 1 Pharmacokinetic Interaction and Dose-Escalation Cohorts

Cohort 1: Six patients will be enrolled in the first cohort in Part 1 to assess the potential effect of osimertinib on the PK parameters of G1T38. Projected dose levels are presented in Table 6-1. Patients will receive a single oral dose of G1T38 200 mg on Cycle 1 Day -16 and blood samples for G1T38 PK evaluation will be collected over the subsequent 48-hour period. Patients will then receive oral osimertinib 80 mg once daily without G1T38 on Cycle 1 Days -14 to -3, and then both G1T38 and osimertinib on Cycle 1 Day -2, after which blood samples for G1T38 PK evaluation will be collected over the subsequent 48-hour period. Osimertinib once-daily dosing will continue on Cycle 1 Day -1 and through the end of the Treatment Phase. On Cycle 1 Day 1, patients will begin G1T38 once-daily dosing, which will continue through the end of the Treatment Phase (note: there is no Day 0 in the study). DLTs will be evaluated from Cycle 1 Day -16 through Cycle 1 Day 28 (the DLT period). An SMC will evaluate all safety and available PK data through the DLT period for Cohort 1 prior to the enrollment of additional cohorts.

Thereafter, additional sequential dose-escalation cohorts may be enrolled using a standard 3 + 3 design and will follow the same schedule as described for the first cohort. All dose escalation/de-escalation recommendations made by the SMC will be based on review of safety and available PK from the DLT period of the current cohort, as well as the cumulative safety data from all patients enrolled. Further details with respect to decision making will be described in the SMC Charter. If a patient is withdrawn prior to completing all of the

assessments during the DLT period for reasons other than toxicity in any cohort in Part 1, the patient will be replaced.

Table 6-1 Projected G1T38 Dose Levels, Part 1

Cohort	G1T38 Dose[a] (mg)
Level 2 dose reduction	100
Level 1 dose reduction	150
1	200
2	300
3	400
4	500
5	650

a Intermediate dose levels may be explored at the discretion of the SMC

The maximum G1T38 dose in this study will not exceed 650 mg/day.

6.1.1.1. G1T38 Dose Evaluation Criteria

In the first Cohort of 6 patients, a relatively low dose of G1T38 will be administered to allow for a sufficient safety window. This low dose of G1T38 is anticipated to be below the maximum tolerated dose (MTD), even if osimertinib increases the systemic exposure of G1T38 (see Section 4.4.2). However, if ≥ 2 of 6 patients experience a DLT, then the MTD will have been exceeded and a lower G1T38 dose level may be explored. If 1 or fewer patient(s) in the first cohort of 6 experience a DLT, then 3 patients may be enrolled at the next SMC recommended G1T38 dose level.

The G1T38 dose evaluation criteria for Cohorts 2 and beyond are listed below.

- If there is no DLT in a given dose level cohort, then 3 patients may be enrolled at the next SMC recommended G1T38 dose level.
- If there is 1 DLT in a given dose level cohort of 3 patients, an additional 3 patients will be enrolled at this G1T38 dose level. If no additional DLTs are observed (ie, ≤ 1 out of 6 with DLT), escalation may proceed to the next SMC recommended G1T38 dose level.
- If there are ≥ 2 DLTs in a given dose level cohort, then the MTD will have been exceeded and a lower G1T38 dose level may be explored as determined by the SMC.

6.1.1.2. Definition of Dose-Limiting Toxicities (Applicable to Cycle 1 Day -16 through Cycle 1 Day 28 in Part 1)

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

- Grade 4 neutropenia
- ≥ Grade 3 neutropenic infection/febrile neutropenia
- Grade 4 thrombocytopenia
- ≥ Grade 3 thrombocytopenia with bleeding
- ≥ Grade 3 nonhematologic toxicity (additional criteria for nausea, vomiting, diarrhea, or fatigue: lasting > 5 days with maximal medical management)

- Liver function test abnormalities meeting Hy's Law criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 3 × upper limit of normal [ULN] and total bilirubin ≥ 2 × ULN). All study drugs must be permanently discontinued in any patient meeting Hy's Law criteria.

Each patient will be evaluated for toxicity during the Treatment Phase. The toxicity of G1T38 administered with osimertinib will be assessed by the investigators using National Cancer Institute (NCI) CTCAE, Version 4.03.

6.1.2. Part 2

In Part 2, eligible patients will be enrolled into a randomized portion of the study. Patients will be randomized (1:1) to receive osimertinib or G1T38 (at the RP2D) + osimertinib. Following screening, patients will begin once daily oral dosing with osimertinib or G1T38 + osimertinib on Cycle 1 Day 1.

Patients who are initially randomized to receive osimertinib alone may crossover to G1T38 + osimertinib at the time of disease progression as determined by blinded independent central review (BICR). Patients should continue osimertinib monotherapy uninterrupted prior to crossover. The date of crossover is defined as the first date the patient receives G1T38 + osimertinib.

An independent data monitoring committee (IDMC) shall review all cumulative safety and efficacy data, as well as all available PK data, approximately every 4 months during the Treatment Phase of Part 2 of the study. The IDMC shall make recommendations regarding continuation of the study, suggested modification of the study, or cessation of the study based on cumulative safety and efficacy data, including cessation for futility. Further details with respect to decision making will be described in the IDMC Charter.

7. STUDY POPULATION

7.1. Selection of Patients

Overall, up to 144 patients may be enrolled in the study.

In Part 1, up to 36 patients may be enrolled.

In Part 2, up to 108 patients will be enrolled.

7.1.1. Inclusion Criteria

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

1. Provision of signed and dated written informed consent prior to any study specific procedures, sampling, and analysis

2. Women or men, 18 years or older

3. Histologic or cytologic confirmed diagnosis of NSCLC

4. Stage IV NSCLC

5. Documented EGFR mutation (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q). Patients in Part 1 that are EGFR TKI treatment naive will be enrolled based on a locally available EGFR mutation test result that has been FDA-approved and performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (US sites) or based on a locally available EGFR mutation test result that has been performed in an accredited laboratory (sites outside of the US).

    a. *Part 2 Only*: Tumor EGFR T790M mutation-positive status after documented disease progression on first-line treatment with a first or second generation EGFR TKI. Patients will be enrolled based on a locally available T790M mutation test result (tumor biopsy or cell-free DNA [cfDNA]) that has been FDA-approved (eg, cobas® EGFR Mutation Test v2, FoundationOne CDx™) and performed in a CLIA-certified laboratory (US sites) or a locally available T790M mutation test result (tumor biopsy or cfDNA) that has been performed in an accredited laboratory (sites outside of the US). Testing for the presence of the T790M mutation in plasma specimens (cfDNA) is recommended only in patients for whom a tumor biopsy cannot be obtained.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks

7. Evaluable disease (Part 1 only) or measurable disease as defined in Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, as determined by the investigator

    - Measurable disease is defined as having at least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), which is suitable for accurate repeated measurements.

8. Left ventricular ejection fraction (LVEF) ≥ institution's lower limit of the reference range

9. Adequate bone marrow reserve or organ function as demonstrated by the following laboratory values:

    a. Hemoglobin ≥ 90 g/L

    b. ANC ≥ 1.5×10^9/L

    c. Platelet count ≥ 100×10^9/L

    d. Calculated creatinine clearance ≥ 50 mL/min (by Cockcroft-Gault formula [Cockcroft and Gault 1976] or ^{51}Cr-EDTA)

    e. Total bilirubin ≤ 1.5 × ULN; < 3 × ULN if the patient has documented Gilbert's disease or liver metastases

    f. ALT < 2.5 × ULN if no demonstrable liver metastases or < 5 × ULN in the presence of liver metastases

    g. AST < 2.5 × ULN if no demonstrable liver metastases or < 5 × ULN in the presence of liver metastases

10. Contraception: Patients must be willing to comply with the requirements for contraception as described in Section 8.10

Additional criteria that apply to Part 2 only:

11. Measurable disease as defined in RECIST, Version 1.1, as determined by the investigator

7.1.2. Exclusion Criteria

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

1. Treatment with any of the following:

    a. EGFR TKIs (erlotinib, gefitinib, afatinib, osimertinib) **within 9 days** of the first dose of study drug; other approved EGFR TKIs within 5 half-lives of the first dose of study drug

b. Investigational agents within 28 days, or 5 half-lives, whichever is longer, of the first dose of study drug; antibody based therapy within 6 weeks of the first dose of study drug

c. *Part 1:* More than 2 prior lines of cytotoxic chemotherapy for advanced NSCLC

d. *Part 2:* Previous treatment with osimertinib or other T790M active EGFR TKI

e. *Part 2:*Any prior cytotoxic chemotherapy for advanced NSCLC

2. Major surgery within 14 days of the first screening visit

3. Blood transfusions or hematopoietic growth factor therapy within 14 days prior of first screening visit

4. Prior radiotherapy treatment to > 25% of the bone marrow or radiotherapy with a wide field of radiation within 28 days of the first dose of study drug

5. Patients receiving medications, herbal supplements, or foods known to be potent inhibitors of CYP3A4 or orally administered sensitive substrates of CYP3A4 within 14 days prior to first dose of study drug, including but not limited to the following:

    a. **Inhibitors**, for example: clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, ritonavir, telithromycin, and verapamil

    b. **Substrates**, for example: astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, everolimus, pimozide, quinidine, sirolimus, and tacrolimus

6. Patients receiving medications, herbal supplements, or foods known to be potent inducers of CYP3A4 within 21 days prior to the first dose of study drug, including but not limited to the following:

    a. **Inducers**, for example: carbamazepine, *Hypericum perforatum* (St. John's wort), phenobarbital, phenytoin, rifampin

7. Patients receiving medications, herbal supplements, or foods known to be potent inhibitors of BCRP within 14 days prior to first dose of study drug, including but not limited to the following:

    a. **Inhibitors**, for example: sulfasalazine, curcumin, turmeric supplements, cyclosporine, eltrombopag

8. *Part 1:* Patients receiving medications that raise gastric pH within 7 days prior to first dose of study drug such as proton pump inhibitors (eg, omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole), H2 blockers (eg, nizatidine,

famotidine, cimetidine, ranitidine), and antacids (eg, sodium bicarbonate, calcium carbonate, aluminum-based antacids, magnesium compounds, alginic acid).

9. Any unresolved toxicities from prior surgeries or therapy of > Grade 1 (CTCAE, Version 4.03) at the time of starting study drug with the exception of alopecia (any grade) and platinum therapy-related peripheral neuropathy (> Grade 2)

10. Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they are currently asymptomatic and clinically stable off anticonvulsants and steroids for at least 28 days prior to first dose of G1T38.

11. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol

12. Known chronic, active infection including but not limited to hepatitis B virus, hepatitis C virus, tuberculosis, and human immunodeficiency virus (HIV); screening for chronic conditions is not required

13. Any of the following cardiac criteria:

    a. Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value

    b. Any clinically important abnormalities in rhythm, conduction, or morphology or resting ECG, eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec

    c. Any factors that increase the risk of QTc prolongation (see Appendix 3 for list of drugs) or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives, or any concomitant medication known to prolong the QT interval

    d. 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)

    e. Known history of stroke, cerebrovascular accident, or myocardial infarction within 6 months prior to first dose of study drug

14. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease

15. Refractory nausea and vomiting, chronic gastrointestinal disease, gastrointestinal ulcer, gastrointestinal bleeding, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of study drug

16. 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

17. History of hypersensitivity to active or inactive excipients of study drug or drugs with a similar chemical structure or class to study drug

18. Women who are pregnant or breastfeeding

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

20. Legal incapacity or limited legal capacity

21. Judgement by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements

22. Prior hematopoietic stem cell or bone marrow transplantation

8. TREATMENTS

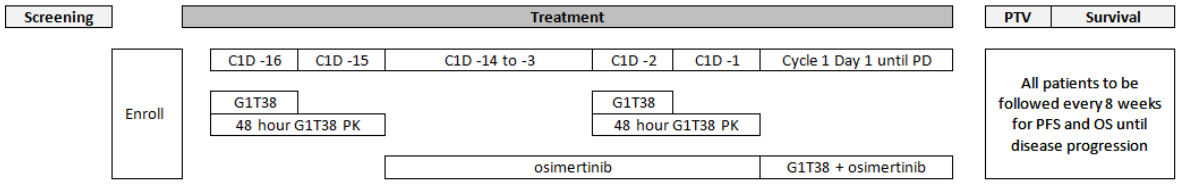
8.1. Treatments Administered

Study drugs will be administered as follows for each cohort in Part 1 of the study:

- Cycle 1 Day -16: single oral dose of G1T38
- Cycle 1 Day -15: no study drug administered
- Cycle 1 Days -14 to -3: oral once-daily doses of osimertinib
- Cycle 1 Day -2: single oral dose of osimertinib and G1T38
- Cycle 1 Day -1: single oral dose of osimertinib

Beginning with Cycle 1 Day 1, oral once-daily doses of G1T38 and osimertinib will commence (Figure 8-1).

Figure 8-1 Study Schema: Part 1

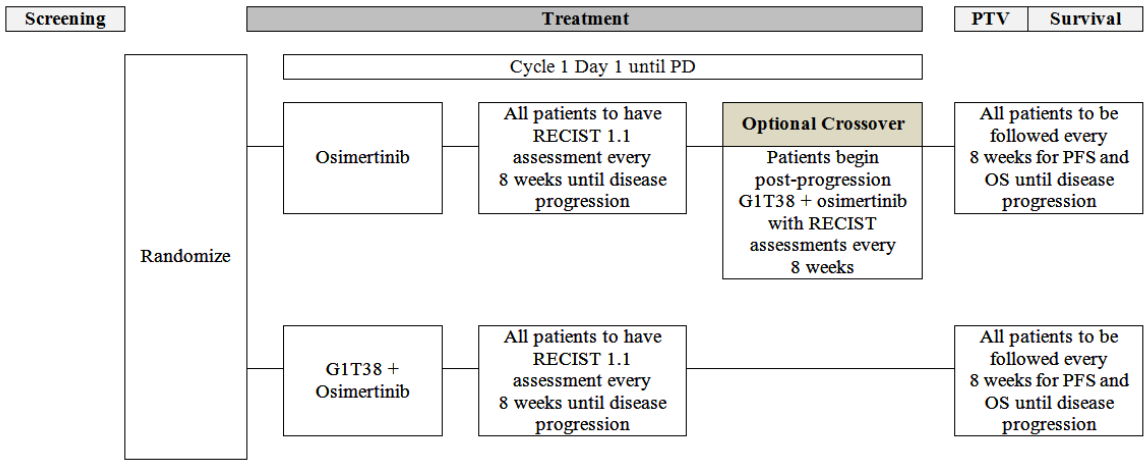


PTV = Post-Treatment visit

There is no Day 0 in the study. A treatment cycle is defined as 28 days.

In Part 2, eligible patients will be randomized (1:1) to receive osimertinib or G1T38 (at the RP2D) + osimertinib. Randomized patients will begin once-daily oral dosing of osimertinib or G1T38 + osimertinib on Cycle 1 Day 1 (Figure 8-2).

Figure 8-2 Study Schema: Part 2



PTV = Post-Treatment visit

8.1.1. Investigational Medicinal Product (IMP)

G1T38 will be initially supplied initially as oral capsules containing 25 or 100 mg equivalents of G1T38 free base. Excipients used in the formulation include microcrystalline cellulose, hypromellose, mannitol, croscarmellose sodium, and magnesium stearate.

Once available, G1T38 supply will be transitioned to oral tablets containing 50 or 200 mg of G1T38 free base. Excipients used in the tablet formulation include microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate. The film coating contains polyethylene glycol: polyvinyl alcohol graft copolymer, talc, titanium dioxide, mono-and di-glycerides, and partially hydrolyzed polyvinyl alcohol.

Alternate strengths may be utilized in the event that they become available.

Packaging and Labeling

G1T38 is packaged in high-density polyethylene (HDPE) bottles and sealed with child-resistant closures. Bottles of G1T38 capsules contain 30 capsules; whereas, bottles of G1T38 tablets contain 35 tablets. Bottles of G1T38 will be labeled and supplied to the investigator or pharmacist/designee who will inventory the contents and document them according to the drug accountability requirements (Section 8.1.4).

Storage

The G1T38 shall be stored at 15°C to 30°C.

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

8.1.2. Other Investigational Medicinal Products

8.1.2.1. Osimertinib

A description of the formulation, packaging and labeling for osimertinib can be found in the respective current prescribing information (see Appendix 2).

Store osimertinib bottles at 25°C (77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F).

8.1.3. Procedure for Dispensing

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

8.1.4. Investigational Product Accountability

The pharmacist/designee will verify the integrity of the clinical study supplies (storage conditions, correct amount received, condition of shipment, bottle numbers, etc.) according to the investigative site's standard operating procedures (SOPs). Additional requirements may be found in the Pharmacy Manual.

8.2. Method of Assigning Patients to Treatment Groups

A unique patient identification number and allocation to a cohort/treatment group will be assigned by an interactive web-response system (IWRS).

8.3. Dose, Dosing Regimen, and Route

8.3.1. G1T38

The starting dose of G1T38 is 200 mg orally (see Section 4.4.2). Dose escalation/ de-escalation is described in Section 6.1.1.1. The maximum G1T38 dose level explored shall not exceed 650 mg per day.

In Part 1, all patients will receive single doses of G1T38 on Cycle 1 Day -16 and Cycle 1 Day -2 and begin continuous G1T38 once-daily dosing on Cycle 1 Day 1 (note: there is no Day 0 in the study). In Part 2, patients randomized to osimertinib with G1T38 will begin G1T38 once-daily continuous oral dosing on Cycle 1 Day 1.

G1T38 should be taken with food. G1T38 should be taken at approximately the same time each day.

8.3.2. Osimertinib

All patients will receive continuous oral osimertinib 80 mg once daily (starting on Cycle 1 Day -14 in Part 1 and on Cycle 1 Day 1 in Part 2).

Osimertinib may be taken with or without food, and should be taken at approximately the same time each day.

8.3.3. Dose Modification

8.3.3.1. G1T38

Dose adjustments of G1T38 for toxicities 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. No more than 2 G1T38 dose level reductions in total are allowed for any patient. Toxicity that requires dose level reduction more than twice will lead to permanent discontinuation of G1T38 dosing for the individual patient.

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

An off-drug period of up to 21 consecutive days is permitted to allow recovery from any toxicity. Off-drug periods of greater than 21 days may be allowed if the investigator believes the potential benefits of continued treatment outweigh the potential risks, but such cases must be discussed with the medical monitor.

Dose Modifications for G1T38-Related Hematologic Toxicity

The G1T38 dose level adjustments in Table 8-1 are based on hematologic adverse reactions, except lymphopenia (unless associated with clinical events, eg, opportunistic infections).

Table 8-1 G1T38 Dose Level Adjustments Based on G1T38-related Hematologic Toxicities

CTCAE Grade of Hematologic Toxicity	G1T38 Dose Adjustment
Grade 3	Continue G1T38 and repeat CBC at next scheduled visit.
≥ Grade 3 neutropenia associated with a documented infection or fever ≥ 38.5°C	Withhold G1T38 and monitor counts weekly until ANC ≥ 1 x 10^9/L. Resume therapy at the next lower dose.
≥ Grade 3 thrombocytopenia associated with bleeding	Withhold G1T38 and monitor counts weekly until platelet count ≥ 75 x 10^9/L. Resume therapy at the next lower dose.
Grade 4	Withhold G1T38 and monitor counts weekly until ANC ≥ 1 x 10^9/L and platelet count ≥ 75 x 10^9/L. Resume therapy at the next lower dose.

ANC = absolute neutrophil count; CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events

Granulocyte-colony stimulating factor

The optimal treatment for G1T38-induced neutropenia is to withhold G1T38. Granulocyte-colony stimulating factor (G-CSF) will not work in this setting because G1T38 induces a G1 cell cycle arrest in myeloid precursors that cannot be overcome by G-CSF. Withholding G1T38 treatment will allow neutrophil counts to recover naturally as the study drug concentrations in the body decline and the myeloid precursors are released from G1 arrest and mature to produce neutrophils. If the patient experiences neutropenia lasting

more than 10 days after the cessation of G1T38 and the investigator believes that G-CSF use is clinically indicated, then the investigator must contact the medical monitor to discuss the use of G-CSF.

In the event that the patient experiences a drug-related hematologic toxicity warranting dose reduction, which may be related to G1T38 or osimertinib (ie, the investigator is unable to determine whether the toxicity is related to G1T38 or osimertinib), the investigator shall dose-reduce G1T38 first. If the toxicity does not resolve following the first dose reduction of G1T38, then the investigator shall use clinical judgement to determine if a second G1T38 dose reduction is warranted or if osimertinib dose reduction is warranted. In this situation, discussion with the medical monitor is recommended.

Dose Modifications for G1T38-Related Nonhematologic Toxicity

For any ≥ Grade 3 G1T38-related nonhematologic toxicity (excluding alopecia) persisting despite optimal medical treatment, withhold treatment with G1T38 until symptoms resolve to Grade ≤ 2 (if not considered a safety risk for the patient). Treatment should be resumed at the next lower dose level of G1T38.

Any patient with liver function test abnormalities meeting Hy's Law criteria (AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN) must have all study drugs permanently discontinued.

Patients with gastrointestinal AEs (eg, nausea, vomiting, diarrhea) may have the total daily dose split, as close to 50:50 as possible, to a morning dose and an evening dose as a means to potentially improved gastrointestinal tolerability. Dose-splitting is not permitted during the DLT evaluation period or the PK evaluation period. In this situation, discussion with the medical monitor is suggested.

8.3.3.2. Osimertinib

Dose modifications for osimertinib for adverse reactions are to be made according to Table 8-2.

If a patient experiences a Grade 3 (CTCAE) or higher and/or unacceptable toxicity (any grade), where the investigator considers the AE of concern to be specifically associated with osimertinib (and not attributable to the disease or disease-related processes for which the patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If a toxicity resolves or reverts to ≤ Grade 2 (CTCAE) within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose or a lower dose using the rules below for dose modifications (Table 8-2) and with discussion and agreement with the sponsor's study team physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤ Grade 2 (CTCAE) after 3 weeks, then osimertinib therapy shall be permanently discontinued and the patient shall be observed until resolution or stabilization of the toxicity.

Patients experiencing any of the following AEs will not be permitted to restart osimertinib treatment:

- Corneal ulceration
- Interstitial lung disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia
- Symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks
- Liver function test abnormalities meeting Hy's Law criteria (AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN). All study drugs must be permanently discontinued in any patient meeting Hy's Law criteria.

Table 8-2 Recommended Dose Modifications for Osimertinib-Related Adverse Reactions

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	Interstitial lung disease/ pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval > 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is < 481 msec or recovery to baseline, then resume at 40 mg dose
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue osimertinib
	Symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks	Permanently discontinue osimertinib
Other	≥ Grade 3 adverse reaction	Withhold osimertinib for up to 3 weeks
	If improvement to Grade 0 to 2 within 3 weeks	Resume at 80 or 40 mg daily (investigator's discretion)
	If no improvement within 3 weeks	Permanently discontinue osimertinib

ECG = electrocardiogram; QTc = QT interval corrected for heart rate

a Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.

Source: Table copied from Table 1 of the osimertinib package insert (see Appendix 2)

In the event that the patient experiences a drug-related hematologic toxicity, which may be related to G1T38 or osimertinib, the investigator shall dose-reduce G1T38 first (refer to Section 8.3.3.1).

In the event that the patient receiving G1T38 + osimertinib experiences an osimertinib-related toxicity requiring permanent discontinuation of osimertinib, the patient may continue G1T38 monotherapy at the discretion of the investigator.

Details regarding the management of specific AEs related to osimertinib are discussed in Sections 8.3.3.2.1 to 8.3.3.2.6.

8.3.3.2.1. Interstitial Lung Disease/Pneumonitis-like Toxicity

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of ILD is observed, an interruption in osimertinib dosing is recommended, and the sponsor study team shall be informed. It is strongly recommended to perform a full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters) to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD shall be considered and osimertinib treatment permanently discontinued.

In the absence of a diagnosis of ILD, osimertinib may be restarted following consultation with the sponsor's study team physician.

8.3.3.2.2. QTc Prolongation

Patients with QTcF prolongation to > 500 msec shall have study treatment interrupted and regular ECGs performed until resolution to < 481 msec, and then restarted at a reduced dose of osimertinib 40 mg. If the toxicity does not resolve to < 481 msec within 21 days, the patient will be permanently withdrawn from osimertinib treatment.

8.3.3.2.3. Keratitis

Keratitis was reported in 0.7% (n = 6) of the 833 patients treated with osimertinib in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye shall be referred promptly to an ophthalmology specialist.

8.3.3.2.4. Changes in Cardiac Contractility

Across clinical trials, LVEF decreases of ≥ 10% and a drop to < 50% occurred in 4.0% (26/655) of patients treated with osimertinib who had baseline and at least 1 follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks, permanently discontinue osimertinib therapy (Table 8-2).

Permanent Discontinuation Due to Toxicity

Patients experiencing corneal ulceration, ILD, symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks, or QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart osimertinib treatment. Any patient with liver function test abnormalities meeting Hy's Law criteria (AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN) must have all study drugs permanently discontinued.

8.3.3.2.5. Skin Reactions

Changes in the CTCAE grade of skin reactions will be collected in the AE eCRF.

Photographs of skin reactions may be collected and these photographs shall be available for central review by the sponsor or designee and for external expert dermatological review if required, if patient consent is obtained.

Skin biopsies may be taken of skin reactions.

8.3.3.2.6. Diarrhea

In the event that the patient experiences drug-related diarrhea, which may be related to G1T38 or osimertinib, the investigator shall dose-reduce G1T38 first (refer to Section 8.3.3.1).

Changes in CTCAE grade of diarrhea will be captured in the AE eCRF.

8.4. Randomization and Blinding

Parts 1 and 2 are open label. In Part 1, no treatment randomization will be required. In Part 2, patients will be randomized (1:1) to receive osimertinib or G1T38 (at the RP2D) + osimertinib. Study drug administration shall begin no more than 96 hours after randomization. Randomization will be stratified according to 2 factors: the presence or absence of CNS metastases at screening and Asian versus non-Asian ethnicity.

8.5. Prior and Concomitant Medications and Procedures

All concomitant medications including prescription medications, over-the-counter preparations, herbal remedies, traditional remedies, growth factors, blood products, and parenteral nutrition taken during the 14 days prior to signing the ICF, during the study treatment, and through the Post-Treatment visit shall be documented in the eCRF.

Administration of concomitant, nonprotocol anticancer therapies prior to disease progression is not permitted during the treatment phase of this study. Concomitant radiotherapy and surgeries may be permitted as described in Section 8.8.

Administration of other concomitant investigational agents for any indication is not permitted during the treatment phase of this study.

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

If medically feasible, patients taking regular medication(s), with the exception of prohibited medications (see below), should be maintained on those medications throughout the study period.

Refer to Appendix 4 for additional details regarding concomitant medications.

8.5.1. CYP3A4 Substrates

G1T38 has the potential to inhibit CYP3A4/5 in both a competitive and time-dependent manner based on in vitro studies. Using the FDA recommended model-based predictions in

the guidance for drug interaction studies (*US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2012*), G1T38 has the potential to significantly inhibit CYP3A4 in the gut and thus may have a clinically significant effect on orally administered CYP3A4 substrates with a narrow therapeutic index and such drugs are prohibited during participation in this study (beginning 14 days prior to first dose of study drug until 14 days after last dose of study drug).

- **Prohibited, orally administered CYP3A substrates with a narrow therapeutic index, including but not limited to the following:**
  - Astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, everolimus, pimozide, quinidine, sirolimus, and tacrolimus
- **Caution** should be used with concurrent use of other orally administered CYP3A substrate drugs with consideration of dose reduction of the substrate if clinical signs and symptoms of toxicity emerge (eg, muscle aches with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors).

The model-based calculation for inhibition of CYP3A4 in the liver predicts a marginal inhibitory effect by G1T38 and therefore the likelihood of a clinically significant drug interaction for CYP3A substrates administered via routes other than oral (eg, intravenous, transdermal, inhalation, etc.) is low.

- **Caution** should be used with concurrent use of non-orally administered CYP3A substrates with a narrow therapeutic index with consideration of dose reduction of the substrate if clinical signs and symptoms of toxicity emerge (eg, increased somnolence with transdermal fentanyl or intravenous midazolam).

8.5.2. CYP3A4 Inhibitors and Inducers

G1T38 is a substrate for CYP3A4, although the extent of metabolism by CYP3A4 is expected to be low in humans since the in vitro clearance of G1T38 in human liver microsomes and hepatocytes was low. G1T38 exposure may be altered by concomitant use of drugs, herbal supplements, or foods that are strong CYP3A inhibitors or inducers and such drugs are prohibited during participation in this study (beginning 14 days prior to first dose of study drug until 14 days after last dose of study drug).

- **Prohibited, strong inhibitors of CYP3A4**, including but not limited to the following: clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, grapefruit juice, telithromycin, diltiazem, verapamil, and ritonavir

- **Prohibited, strong or moderate CYP3A inducers**, including but not limited to the following**:** phenytoin, rifampin, carbamazepine, St John's Wort, phenobarbital, bosentan, modafinil, and nafcillin

In addition, coadministration of osimertinib with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administration of osimertinib alone. Decreased osimertinib exposure may lead to reduced efficacy (Tagrisso Prescribing Information 2017).

Once enrolled, all patients must try to avoid concomitant use of medications, herbal supplements, and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AEs. Such drugs must have been discontinued for an appropriate period before a patient enters screening and for a period of 3 months after the last dose of osimertinib. All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring, and on washout periods is provided in Appendix 4.

8.5.3. BCRP Inhibitors

A primary objective of this study is to assess the effect of osimertinib on the PK of G1T38 via the mechanism of BCRP inhibition by osimertinib. Therefore, patients are prohibited from taking drugs, herbal supplements, or foods that are strong BCRP inhibitors during participation in this study (beginning 14 days prior to the first dose of study drug until 14 days after last dose of study drug).

- **Prohibited, strong inhibitors of BCRP**, including but not limited to the following: sulfasalazine, curcumin, turmeric supplements, cyclosporine, eltrombopag

8.5.4. BCRP substrates

Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication while receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring, and on washout periods is provided in the appendices.

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

8.5.5. Gastric pH Elevating Agents

The solubility of G1T38 is pH dependent. Drugs that raise gastric pH may alter the bioavailability of G1T38 and confound the interpretation of PK data. During Part 1 of the study, concurrent use of medications that raise gastric pH is **prohibited** from 7 days prior to first dose of study drug until after the final PK sample is collected on Cycle 1 Day 1. Such medications include proton pump inhibitors (eg, omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole), H2 blockers (eg, nizatidine, famotidine, cimetidine, ranitidine), and antacids (eg, sodium bicarbonate, calcium carbonate, aluminum-based antacids, magnesium compounds, alginic acid).

8.5.6. CYP2C8 Inhibitors and Inducers

G1T38 is a substrate for CYP2C8, although the extent of metabolism by CYP2C8 is expected to be low in humans since the in vitro clearance of G1T38 in human liver

microsomes and hepatocytes was low. G1T38 exposure may be altered by concomitant use of drugs, herbal supplements, or foods that are strong CYP2C8 inhibitors or inducers.

- **Caution** should be exercised with concomitant use of drugs that are strong inhibitors of CYP2C8 (eg, gemfibrozil, quercetin, sulfinpyrazone, trimethoprim, and nicardipine).
- **Caution** should be exercised with concomitant use of drugs that are strong or moderate inducers of CYP2C8 (eg, rifampin, phenobarbital, and carbamazepine).

8.6. Systemic Corticosteroid Use

Steroids given for physiological replacement (up to 10 mg per day of prednisone or equivalent), as anti-emetics, or by inhalation, ophthalmic, or topical route are allowed. Short courses (up to 21 days) of steroids are allowed to treat acute conditions if medically necessary.

8.7. Supportive Care for Gastrointestinal Adverse Events

Medications to treat gastrointestinal AEs are allowed at any time during the study, as indicated (eg, loperamide for diarrhea, 5-HT3 antagonists for nausea/vomiting, etc.). Such medications shall not be used as primary prophylaxis prior the onset of any gastrointestinal AEs. After a patient has experienced a gastrointestinal AE, supportive treatments may be used as secondary prophylaxis if the patient continues to experience the AE.

8.8. Additional Cautions

G1T38 inhibited P-gp, BCRP, MATE1, MATE2-K, and OCT1 and 2 membrane transporters and therefore caution should be exercised with concomitant use of drugs that are substrates for these transporters (Section 4.2.2; Appendix 4). MATE2-K is involved with tubular secretion of creatinine and inhibition of MATE2-K by G1T38 may cause an increase in serum creatinine levels unrelated to true changes in renal function.

G1T38 is a substrate and inhibitor of P-gp and BCRP efflux transporters. G1T38 exposure may be altered by concomitant use of drugs that are strong inhibitors or inducers of P-gp or BCRP. Caution should be exercised with concomitant use of drugs that are strong inhibitors or inducers of P-gp. Use of strong inhibitors of BCRP during participation in this study is prohibited.

The use of herbal medicine or traditional remedies is not recommended during the active treatment phase.

8.9. Concomitant Radiotherapy or Surgery

Palliative radiotherapy is not allowed within the DLT period. In Part 1 (after the DLT period) and in Part 2, palliative radiotherapy may be permitted to control symptoms (eg, treatment of painful bony lesions or brain or thoracic lesions) provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. Refer to Appendix 6 for additional guidelines on radiotherapy.

Any diagnostic, therapeutic, or surgical procedures performed during the study period shall be documented.

8.10. Contraception

Females

All females of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test result at screening and not be breastfeeding prior to start of dosing.

Females must be either postmenopausal, surgically sterile, or agree to use 2 forms of highly effective contraception from the start of the study until 4 months after discontinuation of study drug.

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

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

True abstinence, when this is in line with the preferred and usual lifestyle of the patient. *Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.*

Postmenopausal is defined as meeting 1, 2, or 3 below:

1. At least 60 years of age and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments OR
2. Medically confirmed ovarian failure OR
3. Younger than 60 years of age **and** have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause **and** have serum levels of estradiol and follicle stimulating hormone within the laboratory's reference range for postmenopausal females

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

Males

If male and sexually active, a condom, with spermicide, must be used with all partners from the start of the study until 4 months after discontinuation of study drug, or must be vasectomized. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuation of study treatment.

8.11. Treatment Compliance

The investigator or designee will dispense the study drug 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. Compliance will be assessed via return of pill bottles and pill counts. The clinical study site will maintain records of G1T38 and osimertinib receipt, dispensing, including the applicable lot numbers, bottle numbers, and pill counts upon return of study drug bottles at clinic visits.

9. STUDY SCHEDULE

The procedures and assessments to be performed during the study are outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2).

Table 9-1 Schedule of Assessments for Part 1

Assessment	Screen-ing	Treatment Phase: Cycle 1 Day -16	Cycle 1 Day -14 (+ 1)	Cycle 1 Day -2 (± 1)	Cycles 1 and 2 Day 1 (+ 2)	Cycles 1 and 2 Day 8 (± 2)	Cycles 1 and 2 Day 15 (± 2)	Cycles 1 and 2 Day 22 (± 2)	Cycle 3 and Every Cycle Thereafter Day 1 (± 3)	Cycle 3 and Every Cycle Thereafter Day 15 (± 3) [as required in Cycle 5 and beyond]	Discon-tinuation	Post-Treat-ment Visit (+10)	Details Provided in Section
Informed consent	X												9.1
EGFR mutation status	X												
Medical/surgical history	X												
Archival tumor sample (if available)	X												10.3
Demographics and baseline characteristics	X												10.6.3
Vital signs	X	X		X	X		X		X		X	X	10.6.3
Inclusion/ exclusion criteria	X												7.1
Physical examination, including weight	X											X	10.6.4
Symptom-directed physical examination		X			X		X		X	X	X		
Height	X												10.6.3
Full ophthalmic examination	X	Perform if the patient experiences any visual symptoms											10.6.6
ECOG performance status	X	X			X				X		X	X	7.1.1
Blood sample for cell-free DNA		X			X (Cycle 2 only)		X (Cycle 1 only)		X (odd Cycles only)			X	10.2

Assessment	Screening	Treatment Phase: Cycle 1 Day -16	Cycle 1 Day -14 (+ 1)	Cycle 1 Day -2 (± 1)	Cycles 1 and 2 Day 1 (+ 2)	Cycles 1 and 2 Day 8 (± 2)	Cycles 1 and 2 Day 15 (± 2)	Cycles 1 and 2 Day 22 (± 2)	Cycle 3 and Every Cycle Thereafter Day 1 (± 3)	Cycle 3 and Every Cycle Thereafter Day 15 (± 3) [as required in Cycle 5 and beyond]	Discontinuation	Post-Treatment Visit (+10)	Details Provided in Section
Pregnancy test	X	X										X	Table 10-5 and 10.6.2; (includes Cycle 5 and beyond decrease in monitoring frequency)
Clinical chemistry	X	X			X		X		X	X	X	X	
Hematology	X	X			X	X	X	X	X	X	X	X	
Urinalysis	X	X			X				X		X	X	
Cystatin C		X	Only if serum creatinine > ULN										
ECG	X	X		X	X (Cycle 2 only)				X		X	X	10.6.5
Echocardiogram/ MUGA scan	X								C3D1 and every third cycle (12 weeks ± 7 days) thereafter				10.6.7
Tumor assessments (RECIST v1.1)	X				After every even cycle (± 7 days) relative to C1D1; after 18 months, every third cycle (± 7 days) relative to C1D1						X		10.1
CT/MRI brain	X				After every even cycle (± 7 days) relative to C1D1 if indicated; after 18 months, every third cycle (± 7 days) relative to C1D1						X		
Optional tumor biopsy at time of progression											X		10.4
Enrollment		X											9.1
Dispense study drug		X			X				X				8.1.3
Dose with G1T38 (Part 1 only)		X		X	Daily dosing with G1T38 beginning on Cycle 1 Day 1								8.1
Dose with osimertinib (Part 1 only)		Daily dosing with osimertinib beginning on Cycle 1 Day -14											
Plasma samples for PK analysis (Part 1)		X		X									10.5.1

Assessment	Screen-ing	Treatment Phase: Cycle 1 Day -16	Cycle 1 Day -14 (+ 1)	Cycle 1 Day -2 (± 1)	Cycles 1 and 2 Day 1 (+ 2)	Cycles 1 and 2 Day 8 (± 2)	Cycles 1 and 2 Day 15 (± 2)	Cycles 1 and 2 Day 22 (± 2)	Cycle 3 and Every Cycle Thereafter Day 1 (± 3)	Cycle 3 and Every Cycle Thereafter Day 15 (± 3) [as required in Cycle 5 and beyond]	Discon-tinuation	Post-Treat-ment Visit (+10)	Details Provided in Section
Concomitant medications and procedures		At every visit											8.5
Adverse events		At every visit											10.6.1

C = Cycle; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal

Table 9-2 Schedule of Assessments for Part 2

Assessment	Screening	Treatment Phase								Details Provided in Section
		Cycles 1 and 2				Cycle 3 and Every Cycle Thereafter				
		Day 1 (± 2)	Day 8 (± 2)	Day 15 (± 2)	Day 22 (± 2)	Day 1 (± 3)	Day 15 (± 3) [as required in Cycle 5 and beyond]	Discon-tinuation	Post-Treatment Visit (+10)	
Informed consent	X									9.1
EGFR mutation status, must be T790M positive	X									
Medical/surgical history	X									
Archival tumor sample (if available)	X									10.3
Demographics and baseline characteristics	X									10.6.3
Vital signs	X	X		X		X		X	X	10.6.3
Inclusion/exclusion criteria	X									7.1
Physical examination, including weight	X								X	10.6.4
Symptom-directed physical examination		X		X		X	X	X		
Height	X									10.6.3
Full ophthalmic examination	X	Perform if the patient experiences any visual symptoms								10.6.6
ECOG performance status	X	X				X		X	X	7.1.1
Blood sample for cell-free DNA		X		X (Cycle 1 only)		X (odd Cycles only)			X	10.2

Assessment	Screening	Treatment Phase								Details Provided in Section
		Cycles 1 and 2				Cycle 3 and Every Cycle Thereafter		Discon-tinuation	Post-Treatment Visit (+10)	
		Day 1 (± 2)	Day 8 (± 2)	Day 15 (± 2)	Day 22 (± 2)	Day 1 (± 3)	Day 15 (± 3) [as required in Cycle 5 and beyond]			
Pregnancy test	X	X (C1 only)							X	Table 10-5 and 10.6.2 (includes Cycle 5 and beyond decrease in monitoring frequency)
Clinical chemistry	X	X		X		X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X				X		X	X	
Cystatin C		X	Only if serum creatinine > ULN							
Electrocardiogram	X	X				X		X	X	10.6.5
Echocardiogram/ MUGA scan	X					C3D1 and every third cycle (12 weeks ± 7 days) thereafter		X		10.6.7
Tumor assessments (RECIST v1.1)	X	After every even cycle (± 7 days) relative to C1D1; after 18 months, every third cycle (± 7 days) relative to C1D1						X		10.1
CT/MRI brain	X	After every even cycle (± 7 days) relative to C1D1 if indicated; after 18 months, every third cycle (± 7 days) relative to C1D1						X		
Optional tumor biopsy at time of progression								X		10.4
Randomization		X								8.4
Dispense study drug		X				X				8.1.3
Dose osimertinib ± G1T38		Daily dosing with osimertinib ± G1T38								8.19.2
Blood samples for G1T38 PK		X (C2 only)		X (C1 only)	X (C1 only)					10.5.1
Concomitant medications and procedures		At every visit								8.5
Adverse events		At every visit								10.6.1

C = Cycle; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal

9.1. Screening Phase

Patients shall be screened no more than 21 days before the first dose of study drug is administered (ie, 21 days prior to Cycle 1 Day -16 in Part 1 or 21 days prior to Cycle 1 Day 1 in Part 2). Written informed consent must be obtained from each patient before the initiation of any screening procedures. After a patient has given informed consent, eligibility will be determined by a review of the inclusion/exclusion criteria (see Section 7.1) and completion of all screening procedures outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2).

Patients that are EGFR TKI treatment naive in Part 1, will be enrolled based on a locally available EGFR mutation test result that has been FDA-approved and performed in a CLIA-certified laboratory (US sites) or based on a locally available EGFR mutation test result that has been performed in an accredited laboratory (sites outside of the US).

For Part 2, tumor EGFR T790M mutation-positive status after documented disease progression on first-line treatment with a first or second generation EGFR TKI is required. Patients in Part 2 will be enrolled based on a locally available T790M mutation test result (tumor biopsy or cfDNA) that has been FDA-approved (eg, cobas® EGFR Mutation Test v2 and FoundationOne CDx™) and performed in a CLIA-certified laboratory (US sites) or a locally available T790M mutation test result (tumor biopsy or cfDNA) that has been performed in an accredited laboratory (sites outside of the US). Testing for the presence of the T790M mutation in plasma specimens (cfDNA) is recommended only in patients for whom a tumor biopsy cannot be obtained.

Available, most recent archival tumor tissue (eg, block or slides) will be collected and banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the CDK4/6 pathway (see Section 10.3). For additional guidance, please refer to the Laboratory Manual.

Concomitant medications will be monitored continuously from the time of informed consent through the Post-Treatment Visit. Adverse events are captured after the first dose of study drug. Medical events that occur prior to first dose of study drug (G1T38 and/or osimertinib) shall be captured on the Medical History page of the electronic case report form (eCRF).

Eligibility will be determined prior to enrollment (Part 1) or randomization (Part 2) and the start of study drug dosing. Eligible patients will be instructed on all protocol requirements, including any restrictions on concomitant medication usage (see Section 8.5).

9.2. Treatment Phase

Adverse events and concomitant medications will be monitored throughout the study.

Study drugs will be administered as described in Section 8.1.

The timing for assessments and procedures to be performed during the treatment period is outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2).

Patients that crossover from the osimertinib group to the G1T38 + osimertinib group following confirmation of radiographic disease progression by BICR shall follow the timing

for assessments and procedures as outlined in Table 9-2 beginning with Cycle 1 Day 1, including tumor assessments, until disease progression on G1T38 + osimertinib.

9.3. Post-Treatment Visit/Early Termination

Patients will return to the study center for a Post-Treatment visit 30 days from the last dose (+ 10 days). The procedures and assessments to be performed at this visit are outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2).

After completing the Post-Treatment visit, patients will enter the long-term Survival Follow-up Phase.

9.4. Survival Follow-up Phase

Follow-up shall be attempted and documented for each patient that is in the long-term Survival Follow-up Phase at least once every 3 months. Follow-up can be via telephone, clinic visits, or by receiving information from a family member or another provider who is administering care. Patients will be followed for survival until at least 50% of the patients enrolled to Part 2 of the study have died. This will be considered the end of study. However, patients who are still receiving treatment at this time shall continue to receive study treatment until the criteria for study drug discontinuation are met.

The following information will be collected for all patients:

- Survival status
- Details of any anticancer treatment

For patients who have not had disease progression at the time of study drug discontinuation, tumor assessments should be performed every 8 weeks until the occurrence of progressive disease or study completion.

9.5. Unscheduled Visits

Additional visits can be performed at the discretion of the investigator.

10. STUDY PROCEDURES AND ASSESSMENTS

10.1. Efficacy Assessments

Clinical sites will perform all radiology assessments according to RECIST version 1.1. Day-to-day patient care decisions will be based upon investigator assessments. Blinded independent central review-determined response according to RECIST version 1.1 will be the primary outcome measure used to determine progression-free survival (PFS) and best overall response (BOR) in Part 2 of this study. All imaging assessments including unscheduled visit scans shall be collected on an ongoing basis and sent to a sponsor-appointed imaging vendor.

The methods used at baseline for assessment of tumor burden [CT or MRI scans of chest and abdomen (including liver and adrenal glands)] must be used at each subsequent follow-up assessment. Any other areas of disease involvement shall be additionally investigated based on the signs and symptoms of individual patients. The baseline assessment shall be performed within 21 days of treatment start. CT or MRI scans obtained prior to informed consent will not need to be repeated if performed within 21 days prior to the first dose of study drug. Subsequent assessments are to be performed after every even cycle (every 8 weeks relative to Cycle 1 Day 1) until objective disease progression. After 18 months of treatment, subsequent tumor assessments shall be performed every third cycle (every 12 weeks ± 1 week) relative to Cycle 1 Day 1. If a patient has a radiological response (CR or PR), a confirmatory radiological assessment shall be performed at least 4 weeks after the response was first noted. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit (± 1 week) and the patient has not progressed, every attempt shall be made to perform the subsequent scans at their scheduled time points. Any other sites at which new disease is suspected shall also be appropriately imaged. In Part 2, patients that crossover from the osimertinib group to the G1T38 + osimertinib group following BICR confirmation of radiographic disease progression shall continue tumor assessments after every even cycle (every 8 weeks relative to the crossover date) until objective disease progression. After 18 months of treatment following crossover, subsequent tumor assessments shall be performed every third cycle (12 weeks ± 1 week) until disease progression.

Patients with known or suspected brain metastases at screening shall have a CT/MRI of the brain prior to starting study drug. These patients shall be followed up on study with repeated CT/MRI assessment, using the same frequency as RECIST assessments. The same modality for CT/MRI shall be used for a patient throughout the study. Brain metastases will be assessed as nontarget lesions (NTLs).

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan shall be declared as the date of progression.

For those patients who have not progressed at the time of study drug discontinuation, tumor assessments should continue every 8 weeks from the previous, regularly scheduled scan until

disease progression or study completion. If the patient does not plan to return for subsequent post-treatment scans and has not had a scan within the prior 4 weeks, perform tumor assessment at the Discontinuation visit.

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

RECIST Version 1.1 - Blinded Independent Central Review Assessment

The BICR of radiological imagining data will be carried out using RECIST version 1.1. All radiological scans for all subjects (including those at unscheduled visits, or outside visit windows) will be provided to the BICR. Prior radiotherapy reports for subjects (at baseline) and information on biopsied lesions will also be provided to the BICR as appropriate. Further details of the BICR will be documented in the Blinded Independent Review Charter.

10.1.1. Tumor Lesions: Identification and Follow-up

10.1.1.1. 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.

10.1.1.2. 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 NTLs and recorded in the eCRF. Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each NTL should be recorded in the eCRF at each follow-up time point. Multiple NTLs in the same organ may be noted as a single item on the eCRF.

10.1.1.3. 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 existing bone lesions, necrosis of a liver lesion) should not be considered new lesions.

10.1.2. Definitions of Tumor Response and Disease Progression

The determination of 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:

10.1.2.1. 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. If a patient has a radiological response (CR or PR), a confirmatory radiological assessment shall be performed at least 4 weeks after the response was first noted.

10.1.2.2. Evaluation of Nontarget Lesions

- **Complete response (CR)**: Disappearance of all NTLs and normalization of tumor marker level. All lymph nodes must be < 10 mm short axis.
- **Non-CR/Non-PD**: Persistence of 1 or more NTLs and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD)**: Unequivocal progression of existing NTLs or the appearance of at least 1 new lesion.
  - To achieve "unequivocal progression" on the basis of nontarget disease, there must be an overall substantial worsening in nontarget disease, such that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status.

If a patient has a CR, a confirmatory radiological assessment shall be performed at least 4 weeks after the response was first noted.

10.1.2.3. Evaluation of Overall Response at Each Time Point

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

Categorization of objective tumor response assessment at each visit will be based on RECIST Version 1.1: CR, PR, SD and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, target lesion tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

Table 10-1 describes the evaluation of overall response at each time point based on target and NTL responses at each time point, as well as the appearance of new lesions. Evaluation of overall response at each time point for patients with NTLs only may be found in Appendix 5.

The BOR is the best response recorded from randomization until disease progression. Confirmation of CR and PR is required as described in Sections 10.1.2.1 and 10.1.2.2.

Table 10-1 Evaluation of Overall Response at Each Time Point for Patients with Target Lesions

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)

10.2. Cell-Free DNA

Blood samples for cfDNA analysis will be drawn at the time points outlined in Table 9-1 and Table 9-2. Beginning with Cycle 3 Day 1, cfDNA samples shall be collected on Day 1 of odd numbered Cycles (ie, Cycles 3, 5, 7, etc.). After 18 months of treatment, subsequent cfDNA sample collection shall be performed every 12 weeks until disease progression.

Part 2 patients that crossover are not required to have blood samples collected for cfDNA at the crossover date.

The samples will be used for analysis related to the effects of G1T38 on the tumor, including correlation with clinical efficacy endpoints. The processed samples may be stored up to 15 years; handling and storage are to be found in the Laboratory Manual.

10.3. Archival Tumor Tissue

If available, archival tumor tissue (eg, block or slides) will be collected and banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the CDK4/6 pathway. For additional guidance, please refer to the Laboratory Manual.

10.4. Optional Tumor Biopsy at Time of Disease Progression

Optional fresh tumor biopsies at the time of disease progression may be collected and banked for analysis of relevant DNA, RNA, and protein markers, such as those involved in resistance pathways. For additional guidance, please refer to the Laboratory Manual.

10.5. Pharmacokinetic Assessments

10.5.1. Pharmacokinetic Sampling

Blood samples for measurement of G1T38 and osimertinib concentrations will be collected as described below and outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2). Information on blood sample collection, handling and storage can be found in the Laboratory Manual.

Part 1

Serial PK blood samples for the measurement of G1T38 concentration in plasma will be collected from all patients in Part 1 on Cycle 1 Day -16 and Cycle 1 Day -2 as outlined in Table 10-2. G1T38 must be administered by clinic staff on Cycle 1 Day -16 and Cycle 1 Day -2.

Pharmacokinetic blood samples for the measurement of osimertinib trough concentration and the G1T38 pre-dose concentration in plasma will be collected from all patients in Part 1 on Cycle 1 Day -2. These samples should be taken **prior to** (within 60 minutes) the morning dose of osimertinib and G1T38. The doses of G1T38 and osimertinib should be taken together, but G1T38 may be given up to 60 minutes after the osimertinib dose.

The actual times of blood sample collections should be documented in the eCRF.

Table 10-2 Part 1: Cycle 1 Day -16 and Cycle 1 Day -2 Blood Sampling Scheme

		Time Point (h) Relative to G1T38 dose on Cycle 1 Day -16 and on Cycle 1 Day -2								
Sample	0 (Pre-dose)	1	2	3	4	6	8	24	32	48
Window	-60 minutes	(± 10 minutes)			(± 20 minutes)			(± 3 hours[a])		

h = hour

Actual times will be recorded in the eCRF.

a Samples must be a minimum of 5 hours apart.

Part 2

Patients Randomized to G1T38 + Osimertinib

Sparse blood sampling for population PK analysis of G1T38 will be collected during Part 2 for patients randomized to G1T38 + osimertinib. The goal of this sparse sampling is to obtain G1T38 steady-state blood samples from participating patients at the following time points/intervals relative to G1T38 dosing: predose and at 1 to 3, 3 to 6, and 6 to 8 hours postdose. Each participating patient should have a total of 4 blood samples taken, 1 during each time point/interval (see Table 10-2).

On Cycle 1 Day 15, patients shall be instructed to not take their G1T38 dose at home as the dose will be administered in the clinic following collection of the predose blood sample. In addition, on Cycle 1 Day 15, a blood sample shall be obtained at 1 to 3 hours postdose. It is strongly encouraged that the site contact the patient via telephone prior to the Cycle 1 Day 15 visit to remind the patient not to take the morning dose of G1T38.

On Cycle 1 Day 22, a blood sample shall be obtained 3 to 6 hours postdose. On Cycle 2 Day 1, a blood sample shall be obtained 6 to 8 hours postdose. It is anticipated that patients will self-administer G1T38 at a range of times during the day and that clinic visits may occur at any time throughout the day during normal business hours. The investigator is encouraged to work with the patient to schedule visits at an appropriate time of day in order to obtain the blood samples during the specified time intervals.

Table 10-3 Part 2 Blood Sampling Scheme for G1T38 Population PK Analysis

Sample	1	2	3	4
Cycle/Day	Cycle 1 Day 15		Cycle 1 Day 22	Cycle 2 Day 1
Time point	Predose	1-3 hours postdose	3-6 hours postdose	6-8 hours postdose
Notes	G1T38 administered in clinic			

10.5.2. Pharmacokinetic Parameters

Pharmacokinetic parameters to be derived for G1T38 [redacted] are listed in Table 10-4. Pharmacokinetic parameters will not be estimated for osimertinib.

Additionally, for Part 2, a population PK model will be developed to estimate the PK parameters of G1T38 [redacted]

Table 10-4 Pharmacokinetic Parameters for G1T38 [redacted]

C_{max}	The observed peak plasma concentration determined from the plasma concentration versus time data
T_{max}	The time to reach the observed peak plasma concentration from the plasma concentration versus time data
λ_z	Terminal phase rate constant, determined by linear regression of at least 3 points on the terminal phase of the log-linear plasma concentration-time curve.
$t_{1/2}$	Terminal half-life, defined as 0.693 divided by λ_z
AUC_{last}	Area under the concentration-time curve from time zero to the last quantifiable concentration using the linear-up log-down trapezoidal rule.
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to infinity using the linear-up log-down trapezoidal rule.
CL/F	Clearance after oral administration, calculated as: $CL/F = Dose/AUC_{0-\infty}$ (G1T38 only)
Vz/F	Volume of distribution in the terminal elimination phase, calculated as: $Vz/F = (CL/F)/\lambda z$ (G1T38 only)
M/P Ratio	Metabolite to parent ratio calculated as $G1T30_{AUCinf}/G1T38_{AUCinf}$

10.6. Safety Assessments

Safety evaluations will begin after the first dose of any study drug and continue throughout the study. Safety evaluations will include monitoring of AEs, vital signs measurements, physical examinations, ECGs, echocardiograms/ multigated acquisition (MUGA) scans, ophthalmic exams, and clinical laboratory assessments.

Toxicity will be graded by the investigators using the NCI CTCAE, Version 4.03.

10.6.1. Adverse Events and Serious Adverse Events

Adverse events are captured following the first dose of study drug. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

10.6.1.1. 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 study drug-related adverse events
- 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 may 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
- Progression of the malignancy under study, including signs and symptoms progression
    - Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE
- Hospitalization due to signs and symptoms of disease progression

An unexpected AE is any AE that is not identified in nature, severity, or frequency in the current IB or product information. The sponsor or designee shall be responsible for determining expectedness; this is not the responsibility of the investigator.

- An Adverse Drug Reaction (ADR) is defined as an AE that is caused by a drug (aka drug-related AE). 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 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 adequately capture all 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.

10.6.1.2. Definition of Serious Adverse Event

The International Council for Harmonisation (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 10.6.1.9) 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.

Hy's Law

Prompt reporting (via the SAE expedited reporting system) of cases meeting Hy's law criteria (AST or ALT $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria. Any patient with liver function test abnormalities meeting Hy's Law criteria must have all study drugs permanently discontinued.

Additional Reporting Requirements for Osimertinib

The following will also be reported to pharmacovigilance: any osimertinib overdose; if a patient taking osimertinib begins lactating; or if a male patient taking osimertinib fathers a child during the treatment period, including the Post-Treatment Follow-up visit. If these events also meet the criteria to be considered an SAE, they shall be reported as such.

Handling of Deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as described below.

Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study

Where death is not clearly due to disease progression, the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results (with translation of important parts into English) shall be reported, if possible, to the sponsor.

10.6.1.3. 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).

10.6.1.4. Assessment of the Causal Relationship of Adverse Events to Study Drug

The investigator will assess causal relationship between study drug and each Adverse Event and classify each AE as either related or unrelated. In determining if an AE is study drug related, the Investigator shall take into account the following question: "Is there a reasonable possibility that the event may have been caused by the study drug?" Investigators shall use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related or unrelated to study drug. The following guidance shall be taken into consideration when determining causality:

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

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

- **Unrelated**: There is not a temporal relationship to study drug administration (eg, too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.
- **Related**: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug, and recurs with re-challenge, when clinically feasible.

For patients receiving combination therapy, causality will be assessed individually for each study drug.

10.6.1.5. Assessment of the Outcome of Adverse Events

The outcome will be assessed according to the following:

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

- Unknown

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

Adverse events and SAEs are reported following the first dose of study drug through 30 days after last dose of study drug (ie, the Post-Treatment Visit).

10.6.1.7. 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 10.6.1.2) will be additionally documented on the SAE report form.

10.6.1.8. 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 MedDRA as specified in the statistical analysis plan (SAP).

10.6.1.9. Reporting of Serious Adverse Events

The reporting period for SAEs begins from the time of first dose of study drug through and including 30 calendar days after the last administration of G1T38. 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 PPD Pharmacovigilance. SAEs that occur prior to the first dose of study drug that are a direct result of a study-related procedure shall additionally be reported as an SAE to PPD Pharmacovigilance.

SAE information will be collected on the eCRFs, therefore it is imperative that any SAE be entered onto the electronic SAE Form within 24 hours of learning of the event. 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:

North America

24 hour Safety Phone: 1-888-483-7729
24 hour Safety Fax: 1-888-529-3580

EMEA/APAC

24 hour Safety Phone: +44 1223 374 240
24 hour Safety Fax: +44 1223 374 102

10.6.1.10. 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 SAE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to the study drug. While the study is ongoing, all deaths should be reported via the electronic data capture system regardless of relationship to study drug, even if the patient has discontinued participation in the study.

After study conclusion, the investigator should notify the sponsor of any death or SAE they are aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to the study drug. The sponsor 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.

10.6.1.11. Regulatory Aspects of Adverse Event Reporting

The sponsor or its representative will report the following suspected unexpected serious adverse reactions (SUSARs) to the independent ethics committee (IEC)/institutional review board (IRB) in an expedited time frame:

- SUSARs that have arisen in the current clinical study that was assessed by the IEC/IRB

The sponsor or its representative will report all SUSARs to the Competent Authority, the Medicine Evaluation Board, and the Competent Authorities in other Member States, if applicable in an expedited time frame.

SUSARs that are already reported to the European Medicines Agency Eudravigilance database do not have to be reported again to the Competent Authority and the Medicine Evaluation Board because they have direct access to the Eudravigilance database.

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.

It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report.

10.6.1.12. Handling of Overdose

In the context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol.

If an overdose on a study drug occurs in the course of the study, then the investigator or other site personnel shall inform the appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated sponsor representative shall work with the investigator to ensure that all relevant information is provided to the sponsor or designee.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 10.6.1.9.

G1T38

A maximum tolerated dose of G1T38 has not been established.

There is no specific treatment in the event of G1T38 overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

Osimertinib

A maximum tolerated dose has not been established for osimertinib.

Such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

There is no specific treatment in the event of osimertinib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

10.6.1.13. Reporting of Pregnancies

Pregnancy 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. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

Each pregnancy, including ectopic pregnancy, which occurs during the course of the study and within 6 weeks of the last dose of study drug, in a study patient or partner of a study patient must be reported to the safety team within 24 hours of learning of its occurrence. If a patient becomes pregnant, all 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 and documented, even if the subject was discontinued from the study.

The avoidance of pregnancy or fathering a child (including sperm donation) is recommended for 4 months following the discontinuation of study drug. Pregnancy of the subject's partner is not considered to be an AE. No information is currently available regarding the effects of G1T38 on fertility, gestation, or subsequent child development.

To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

10.6.2. Clinical Laboratory Assessments

Blood samples will be collected for clinical laboratory assessments as outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2). Hematology, clinical chemistry, and urinalysis samples may be obtained up to 48 hours prior to the scheduled visit. If screening hematology, clinical chemistry, and urinalysis assessments have been performed within 7 days of Cycle 1 Day -16 for Part 1 or within 7 days of Cycle 1 Day 1 for Part 2, then these tests do not have to be repeated prior to commencing first treatment with study drug as long as the patient's clinical condition has not changed. After baseline assessment (Day -16 in Part 1, Cycle 1 Day 1 in Part 2), Cystatin C shall be evaluated only in the event that the serum creatinine is elevated. The measurement of Cystatin C to estimate glomerular filtration rate is included in this study because G1T38 may inhibit MATE transporters in the renal tubule and induce a nonpathologic increase in serum creatinine. The clearance of Cystatin C is not dependent upon the MATE transporters and thus can help differentiate the effect of G1T38 on the MATE transporter from a true decline in renal function.

Absolute neutrophil counts will be monitored weekly for the first 8 weeks (2 cycles), then every 2 weeks for the next 2 cycles. Beginning with Cycle 5 Day 1, patients with stable ≤ Grade 2 hematologic parameters may have hematology monitored monthly on Day 1 of each cycle; patients that do not meet this criteria will continue to have every other week assessment of hematologic parameters.

Clinical chemistry will be monitored every 2 weeks for the first 4 cycles. Beginning with Cycle 5 Day 1, clinical chemistry will be monitored monthly on Day 1 of each cycle.

Clinical laboratory tests to be performed are presented in Table 10-5.

Table 10-5 Clinical Laboratory Tests

Hematology Hemoglobin Hematocrit WBCs with differential Platelets	**Chemistry** Albumin Alkaline phosphatase Total bilirubin Calcium Chloride Creatinine Glucose Inorganic phosphorus Potassium Total protein ALT AST Lactate dehydrogenase Sodium Blood urea nitrogen/urea Cystatin C[a]
Urinalysis Specific gravity pH Glucose Protein Bilirubin Ketones Leukocytes Hemoglobin Microscopic examination (including RBC, WBC, and casts will be performed, if necessary)	**Pregnancy test** Blood or urine tests are acceptable based on the site's standard clinical practice; applicable to women of childbearing potential only.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RBC = red blood cell; WBC = white blood cell

a Postbaseline Cystatin C to be evaluated in the event that serum creatinine is elevated

If treatment is interrupted, the patient should still complete all clinical laboratory assessments as scheduled, as well as on the actual dosing day when treatment is reinitiated.

Laboratory parameters shall be analyzed by a local certified laboratory and a report of the laboratory values shall be sent to the study center. The investigator shall review the laboratory report promptly after receipt of the results and indicate the clinical significance of all abnormal values, and subsequently sign and maintain the laboratory report with the patient's source records/charts. Laboratory parameters for which clinically significant values are noted shall be re-measured on the appropriate clinical follow-up arranged by the investigator. Any laboratory value that remains abnormal at the end of the study and that is considered clinically significant shall 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 shall be assessed using the NCI CTCAE, Version 4.03 (see Appendix 1).

Laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 10.6.1.

The SMC/IDMC may modify the frequency of laboratory monitoring based on cumulative safety data.

10.6.3. Demographics and Vital Signs

The following will be collected at the time points outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2):

1. Height in centimeters (cm)
2. Body weight in kilogram (kg)
3. Body temperature (Celsius)
4. Systolic and diastolic blood pressure, pulse rate, and respiration rate; blood pressure should be assessed after 5 minutes of rest and should be assessed predose

10.6.4. Physical Examination

Physical examinations will be performed at the time points outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2).

Full physical examination evaluations at screening and the Post-Treatment visit shall include general appearance, skin, neck, eyes, ears, nose, throat, lungs/respiratory, heart/cardiovascular, abdomen, back, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological examinations. Subsequent physical exams shall be symptom directed and include body systems as appropriate.

Clinically significant findings on physical examination prior to administration of the first dose of study drug must be recorded as medical history in the eCRF. Clinically significant findings on physical examination made after the first dose of study drug, which meet the definition of an AE, must be recorded as an AE in the eCRF.

10.6.5. Electrocardiogram Assessments

All patients will have three 12-lead ECGs performed at the visits indicated in Table 9-1 (Part 1) and Table 9-2 (Part 2).

Part 1 ECG requirements are as follows:

Cycle and Day	Time Points
Screening	Anytime during visit (one set of 3 ECGs)
Cycle 1 Day -16	Predose and at 2 and 6 hours (± 15 minutes) after the G1T38 dose
Cycle 1 Day -2	Predose and at 2 and 6 hours (± 15 minutes) after the G1T38 dose
Cycle 2 Day 1 and Day 1 of each cycle thereafter	Anytime during visit (one set of 3 ECGs)

Patients enrolled in Part 2 of the study will have three 12-lead ECGs performed at screening and Day 1 of each cycle.

A 12-lead ECG will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated and should be recorded at 25 mm/sec. All ECGs shall be recorded with the patient in the same physical position. The three ECG recordings shall be taken within an approximate 5 minute period. A standardized ECG machine shall be used

and the patient shall be examined using the same ECG machine throughout the study if possible.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it must be reported as a concurrent condition. For all ECGs, details of rhythm, ECG intervals, and an overall evaluation will be recorded.

ECG data shall be collected digitally and shall be transferred electronically for central analysis. The investigator may choose to perform a nondigital ECG at the time of the screening visit in order to identify patients eligible for study entry. If a nondigital ECG is performed at the screening visit it cannot subsequently be used as a baseline recording, in this situation an ECG will need to be collected on the baseline visit in digital form.

Heart rate, PR, R-R, QRS, and QT intervals will be determined and reviewed during central analysis by an external cardiologist.

If there is a clinically significant abnormal ECG finding during the Treatment Phase, this should be recorded on the AE eCRF, according to standard AEs collection and reporting processes. A 30-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

The investigator or designee shall review the ECGs for any abnormalities as compared with the baseline ECGs.

10.6.6. Ophthalmic Examination

Full ophthalmic assessment, including slit-lamp examination, shall be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated (Table 9-1 [Part 1] and Table 9-2 [Part 2]). Ophthalmology examination results shall be recorded in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for central review by the sponsor and sponsor representatives if necessary.

Patients experiencing corneal ulceration will not be permitted to restart study treatment.

10.6.7. Echocardiogram/MUGA

An echocardiogram/MUGA scan to assess LVEF shall be performed at the time points outlined in Table 9-1 (Part 1) and Table 9-2 (Part 2). The modality of the cardiac function assessments must be consistent throughout the study for an individual patient (ie, if echocardiogram is used for the screening assessment then echocardiogram shall also be used for subsequent scans). The patients shall also be examined using the same machine and operator whenever possible. A 30-day (+10 days) follow-up assessment will be required if an on treatment assessment was abnormal and clinically significant at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

10.7. Biomarker Analysis

The subject's consent to the use of donated biological samples is mandatory.

10.8. Appropriateness of Measurements

The measures of efficacy, PK, and safety evaluated in this study are based on the mechanism and activity of G1T38 and standard types of assessments typically performed in patients with NSCLC. 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.

11. STUDY TERMINATION OR STUDY DRUG DISCONTINUATION

11.1. 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

11.2. Site Termination

A study site may 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.

11.3. Discontinuation of Study Drug

Study drug(s) shall be discontinued if any of the following events occur during the study:

- A patient suffers an AE that, in the judgment of the investigator, sponsor, or medical monitor, presents an unacceptable risk to the patient (see Section 8.3.3.2 for additional details).
- 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 radiographically documented or clinically determined disease progression, with the exception of patients in Part 2 that crossover from osimertinib alone to G1T38 + osimertinib at the time of disease progression.

In the event of study drug discontinuation, patients shall be strongly encouraged to complete all scheduled assessments; the Post-Treatment Visit; and the Survival Follow-up Phase of the study. A patient who discontinues study drug for reasons other than PD shall have a CT or MRI scan at the Post-Treatment Visit, if they have not had a scan within the prior 4 weeks and the patient does not plan to return for subsequent post-treatment scans.

When discontinuation is due to a SAE or a Grade 3 or 4 toxicity considered to be related to study drug, the investigator shall follow the event until resolution, return to baseline, or it is deemed that further recovery is unlikely.

In the event a patient discontinues due to an AE or pregnancy, the investigator shall notify the medical monitor or PPD Safety Services by telephone within 24 hours of study drug discontinuation.

11.4. 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.

All data and lab samples collected prior to the date of withdrawal of consent will remain in the clinical database and at laboratory vendor.

12. STATISTICS

Full details on the statistical analyses to be performed will be provided in a separate Statistical Analysis Plan (SAP).

12.1. Sample Size and Power

It is estimated that up to 36 patients will be enrolled in the dose-escalation part of the study (Part 1). The actual number of patients will depend on the number of dose levels/cohorts that are tested.

For the randomized part of the study (Part 2), it is assumed that the overall 1-sided type I error rate is 0.1 and the type II error rate used to compute sample size is 0.20 (corresponding to 80% power). Patients will be randomized using a 1:1 treatment allocation ratio between the 2 treatment groups (osimertinib versus G1T38 + osimertinib).

Assuming a 10.1 month median PFS for the osimertinib group from historical data (Mok et al, 2017) and a hazard ratio (HR) of 0.6 (corresponding to a median PFS of 16.8 months for the G1T38 + osimertinib group), the required number of PFS events is 70. Assuming an accrual period of 12 months and an additional follow-up period of 18 months after the last patient is enrolled, the calculated total sample size for Part 2 is 98 patients. Allowing for a dropout/ lost-to-follow-up rate of approximately 10% gives an adjusted total sample size of 108.

These calculations were carried out using the POWER procedure in SAS® Version 9.4.

12.2. General Considerations

12.2.1. Analysis Populations

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

The full analysis set (FAS) includes all patients who received at least 1 dose of study drug. Analyses using the FAS will be conducted on the basis of the assigned treatment. All efficacy analyses will be assessed using the FAS and the FAS is the primary analysis set for efficacy analysis. The FAS will only be applicable for the Part 2 of the study.

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

The per-protocol (PP) analysis set will include all patients in the safety analysis set who have no major protocol deviations and who received the treatment to which they were randomized. For patients who took the wrong treatment for Part 2 of the study, their data will be excluded from the PP analysis set. The PP analysis set may be used to analyze selected endpoints to

test the robustness of results. The criteria for inclusion in the PP analysis set will be finalized and documented prior to database lock.

The PK analysis set will include all dosed patients with evaluable PK data; it will be the basis of PK-related summaries.

12.2.2. Timing of Analyses

12.2.2.1. Interim Safety Reviews

Following completion of data collection for each dose cohort of Part 1, the SMC will review all safety and available PK data in order to determine the subsequent dose level. At the end of Part 1 of the study, the SMC will review all cumulative safety and PK data in order to determine the RP2D.

12.2.2.2. Independent Data Monitoring Committee

During Part 2, an IDMC will evaluate accumulating safety data according to a charter that defines its roles and responsibilities. The IDMC will perform interim reviews approximately every 4 months during the Part 2 of the study, depending upon the enrollment rate. Additional reviews may occur based on IDMC requests. The IDMC shall make recommendations regarding continuation of the study, suggested modification of the study, or cessation of the study based on cumulative safety and efficacy data, including cessation for futility. The committee will consist of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, NSCLC), clinical pharmacology, 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, will be described in the IDMC charter.

12.2.2.3. Final Analysis

The final analysis will utilize data obtained by BICR and will be conducted after at least 70 PFS events (65%) have occurred or 18 months after the end of accrual for Part 2 of the study, whichever occurs first.

12.2.2.4. End of Study Analysis

The Survival Follow-up Phase will continue until at least 50% of the patients in Part 2 have died. If the Follow-up Survival Phase of the study continues after the final analysis, a supplementary analysis will be done at the time of study completion. Reported results will be cumulative in nature, including all data collected during the entire study.

12.2.3. General Considerations for Data Analysis

Detailed methods of statistical analyses will be presented in the SAP. All statistical analyses will be performed using SAS® Version 9 or higher.

In general, data will be summarized separately by study part (Part 1 and Part 2). Data from Part 1 will be summarized descriptively by dose level, if applicable, and overall. Data from Part 2 will be summarized descriptively by treatment group and overall. Treatment differences between treatment groups for Part 2 will be calculated as G1T38 + osimertinib minus osimertinib alone. Selected safety summaries will include combined data from both Parts 1 and 2 of the study.

The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include mean, median, standard deviation (StD), and minimum and maximum values. The descriptive summaries of time-to-event data will include median, 25% and 75% percentiles, and standard error. The Kaplan-Meier method will also be used to summarize the time-to-event data. All data will be listed for all patients. All confidence intervals (CIs) for treatment differences between treatment groups for Part 2 will be 2-sided 80%, and other CIs will be 2-sided 95%, unless stated otherwise.

Part 1 of the study is descriptive in nature. For the Part 2 of the study, all statistical tests will be conducted at a 1-sided significance level of 10% unless otherwise specified (G1T38 + osimertinib versus osimertinib alone). Where appropriate, model based point estimates, together with their 80% CIs will be presented along with the 1-sided p-value for the test.

12.3. Part 1 (Phase 1b) Statistical Analyses

The primary analysis is based on the assessment of safety and tolerability endpoints for Part 1 of the study. The data will be analyzed by descriptive statistics. All CIs of data summary will be 2-sided 95%, unless stated otherwise.

Adverse event data will be coded to system organ class and preferred term using MedDRA (Version 17.1 or later). The number and percentage of patients experiencing any TEAE, overall, and by system organ class and preferred term will be tabulated. Adverse events related to treatment will be further summarized by the treatment to which it is attributed (eg, G1T38 or osimertinib). DLTs and withdrawals due to AEs will be summarized or listed; further details with respect to these events can be found in Section 6.1.1.2 and 11.3. Severity will be tabulated based on greatest severity observed for each patient. If a patient experiences an AE more than once during the study, the greatest severity will be tabulated.

Any AE occurring within the defined 30 day follow-up period after the last dose of study drug will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study drug) will be flagged in the data listings. AEs occurring after the 30 day follow-up period after last dose of study drug will be listed separately, but not included in the summaries.

12.3.1. Other Safety Endpoints

Observed values and changes from baseline in vital signs, ECG readings, echocardiogram/MUGA scan results, and hematology, clinical chemistry, and liver function parameters will be tabulated at each visit. Toxicities for clinical labs will be characterized according to CTCAE, Version 4.03. Shifts in toxicity grades from baseline to each visit, and

from baseline to the worst grade during the study will be summarized. Summaries examining maximum and minimum post-baseline changes will consider both scheduled and unscheduled data.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. For example, graphical presentations of average changes over time will provide additional focus to be placed on neutrophils and platelet data.

Dose reductions/modifications, interruptions, compliance, and patient exposure will be summarized for each study therapy component, where appropriate.

12.3.2. Efficacy Endpoints

Antitumor efficacy endpoints include the following:

- Best overall response (BOR) according to RECIST v1.1
- Objective response (OR) (CR or PR) according to RECIST v1.1
- Duration of OR, and time to first objective response according to RECIST v1.1
- Clinical benefit rate (CBR) according to RECIST v1.1
- Progression-free survival (PFS) according to RECIST v1.1
- Overall survival (OS)

BOR will be determined using visit responses up until the last evaluable overall visit response prior to or on the date of (i) radiographic or clinical disease progression; (ii) withdrawal of consent to obtain scans; or (iii) receiving subsequent anticancer therapy, whichever is earlier. At each tumor assessment visit, an overall time point response by RECIST 1.1 will be determined programmatically - using the information from target lesions, NTLs, and new lesions.

For patients who progress and subsequently have a response, then the best objective response is only derived from assessments up to and including the time of the progression (ie, it will not include the response after the patient has progressed).

When the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR for a patient, then 2 ways of assigning BOR will be implemented in the analysis. In the primary analysis, BOR will be assigned as SD according to RECIST 1.1, which requires confirmation of CR and PR; in the other method, 2 or more response categories will be added as unconfirmed CR and unconfirmed PR. Both ways of assigning BOR will be implemented in the analysis.

Objective response will be derived as No/Yes (0/1) variable. Patients with a BOR of confirmed CR or PR will be assigned “Yes”. Patients not having a BOR of confirmed CR or PR will be assigned “No.” Hence, objective response rate (ORR) is defined as the proportion of patients with objective response being “Yes.”

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR or SD at the 8 week (end of Cycle 2) or later assessment. A patient will

be considered to have a SD for 8 weeks or longer if a SD response is recorded at 8 weeks or later from first date of study drug administration.

Duration of Objective Response (DOR) is the time between first objective response of CR or PR and the first date that progressive disease is objectively documented or death. Patients who do not experience objective PD or death will not be included in the analysis.

Time to first objective response is the time from first dose of study drug to first objective response of CR or PR. Patients who do not experience objective response of CR or PR will be censored at the last adequate assessment date.

PFS is defined as the time (number of months) from date of first dose of study drug until date of documented disease progression or death due to any cause, whichever comes first. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) radiographic or clinical disease progression; (ii) withdrawal of consent to obtain scans; or (iii) receiving subsequent anticancer therapy, whichever is earlier. Death is always categorized as a confirmed PD event. Censoring methods for patients who do not experience PD or death will be described in the study SAP.

OS is calculated as the time (number of months) from date of first dose of study drug to the date of death due to any cause. Patients who do not experience fatalities during the course of the study will be censored at the date last known to be alive. Patients lacking data beyond the day of first dose of G1T38 will have their survival time censored at day of first dose. OS will not be censored if a subject receives other antitumor treatments after the study drugs.

The BOR, ORRs, and CBR and their corresponding 95% exact CIs will be calculated by Clopper-Pearson method. DOR, time to first objective response, PFS, and OS will be analyzed based on time-to-event summary method. For PFS and OS, Kaplan-Meier estimates will be plotted and tabulated at selected landmark time points (ie, 6 months, 1 year, 1.5 years, and 2 years).

12.4. Part 2 Statistical Analyses

For Part 2 of the study, the primary efficacy endpoint is PFS assessed by BICR according to RECIST 1.1. Other antitumor efficacy endpoints include the following:

- BOR according to RECIST 1.1
- OR (CR or PR) according to RECIST 1.1
- Duration of OR, and time to first objective response according to RECIST 1.1
- CBR according to RECIST v1.1

The derivation of these endpoints follows the similar practice as described in Section 12.3.2, except for the following:

- For the CBR, a patient will be considered to have SD if an SD response is recorded at the 8 week (end of Cycle 2) or later assessment from the date of randomization
- Both PFS and OS are measured from date of randomization

- For those patients who have crossed over from osimertinib to G1T38 + osimertinib in Part 2, the date of first dose of G1T38 administered during the crossover period will be utilized as a reference data for endpoint derivations

Because patients who progressed on osimertinib alone are allowed to crossover to G1T38 + osimertinib, there will be 4 types of summaries for PFS and other antitumor efficacy endpoints (with the first one being the primary source) as follows:

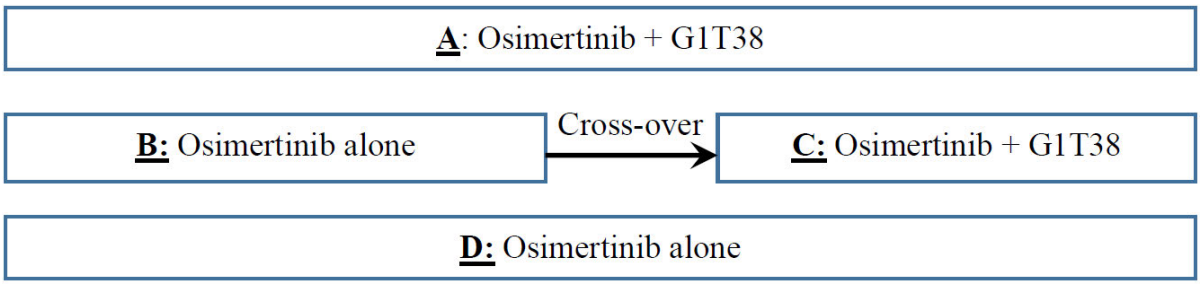
1. Summaries and listings based on assessments collected in the randomized portion of the study (ie, A versus B + D in Figure 12-1).

2. Summaries and listings based on assessments collected in the randomized portion of the study (ie, A versus D in Figure 12-1).

3. Summaries and listings based on assessments collected in the randomized portion of the study for the G1T38 + osimertinib group and crossover portion for the osimertinib alone group (ie, A versus C in Figure 12-1).

4. Summaries and listings based on assessments collected in the crossover portion (ie, C alone in Figure 12-1).

Figure 12-1 Categories of Source Data for Patients



For time-to-event data such as PFS and OS, the 1-sided stratified log-rank test, stratified by presence of CNS metastases (yes versus no) and ethnicity (Asian versus non-Asian), will be used to test the null hypothesis that the distributions in the 2 treatment groups are equal. A Cox regression analysis with a fixed effect for treatment arm and stratification factors will be used to estimate the HR and its 80% CI. Kaplan-Meier estimates will be plotted and tabulated at selected landmark time points (ie, 6 months, 1 year, 1.5 years, and 2 years). The median value and a 95% CI will also be provided (assuming the median can be estimated).

For the overall tumor response data such as ORR and CBR, the 1-sided stratified CMH test will be used to compare the 2 treatment groups. The odds ratio and its associated 80% CI will be presented.

Patients who progressed on osimertinib alone are allowed to crossover to G1T38 + osimertinib. Despite the crossover design, the primary analysis of OS (ie, A versus D + (B + C) in Figure 12-1) will use the strict intention-to-treat (ITT) approach based on FAS, ie, "analyze as randomized" and ignore the treatment switch following progression (and ignore additional anticancer therapies administered after study drug discontinuation). This approach

represents a gold standard. However, osimertinib patients who switch to G1T38 + osimertinib after disease progression may benefit from the delayed administration of G1T38; therefore, the survival treatment estimate becomes confounded. Under such circumstances, the statistical test of the treatment effect is known to be biased towards the null hypothesis of no difference (Robins and Tsiatis 1991; Korhonen et al 1999; Greenland et al 2008). Therefore, 2 additional supportive analyses will be performed to obtain an estimate of survival treatment effect corrected for treatment crossover: rank-preserving structural failure time (RPSFT) method and Cox model with inverse probability of censoring weighting (IPCW). More detailed information will be provided in SAP.

In terms of OS, there will be 3 additional types of summaries as follows:

1. Summaries and listings based on assessments collected in the randomized portion of the study (ie, A versus D in Figure 12-1)

2. Summaries and listings based on assessments collected in the randomized portion of the study for group of G1T38 + osimertinib and crossover portion for group of osimertinib alone (ie, A versus C in Figure 12-1)

3. Summaries and listings based on assessments collected in the crossover portion (ie, C alone in Figure 12-1).

Moreover, post progression survival will be evaluated for A versus D and C versus D in Figure 12-1, and it is calculated as the time (number of months) from the date of first documented progression to the date of death due to any cause, or to the date of last contact (censored observation). For patients who progress on osimertinib alone and crossover to G1T38 + osimertinib, the date of first documented progression on osimertinib alone will be used for the analysis. Patients without documented progression will be excluded from the post progression survival analysis.

In addition, potential influences of baseline patient characteristics such as age, ECOG performance status, and selected biomarkers on the endpoints may be evaluated to compare the treatment groups.

12.4.1. Safety evaluation

The assessment of safety will be based mainly on the frequency of TEAEs and on the number of laboratory values that fall outside of predetermined ranges according to CTCAE, Version 4.03. Other safety data (eg, ECG, vital signs, and echocardiogram/MUGA scan results) will be considered as appropriate.

Dose reductions/modifications, interruptions, compliance, and patient exposure will be summarized for each study therapy component, where appropriate.

Since patients who progressed on osimertinib alone are allowed to crossover to G1T38 + osimertinib, there will be 3 types of safety summaries (with the first one being the primary source of safety assessment) as follows:

1. Safety summaries and listings based on assessments collected in the randomized portion of the study (ie A versus B + D in Figure 12-1).

2. Safety summaries and listings based on assessments collected in the randomized portion of the study and crossover portion (ie, A + C versus B + D in Figure 12-1).

3. Safety summaries and listings based on assessments collected in the randomized portion of the study for the G1T38 + Osimertinib group and the crossover portion for the osimertinib group (ie, A versus C in Figure 12-1).

These outputs will use the safety analysis set (see Section 12.2.1 for definition). The safety summary tables will include only assessments collected no later than 30 days after the last dose of study drug during randomized portion. For those patients who have crossover, the date of first dose G1T38 administered during the crossover period will be utilized to define treatment-emergent. All safety assessments collected before crossover will be listed, those collected later than 30 days after the last dose of study drug during randomized portion, and those collected during the crossover portion will be flagged.

12.5. Pharmacokinetic Analysis

Pharmacokinetic analyses in Part 1 will be based on the PK analysis set, and all analysis and reporting of plasma concentration and PK parameter data will be performed separately for each analyte. Blood samples for PK analysis will be collected as outlined in Table 9-1 to determine G1T38, [redacted] and osimertinib plasma concentrations. Plasma concentration data will be tabulated descriptively and graphed at each visit and time point.

The pharmacokinetic parameters for G1T38 [redacted] presented in Table 10-4 will be calculated with noncompartmental methods (WinNonlin Version 6.3 or higher) based on the plasma concentration-time data. Pharmacokinetic parameters will be summarized descriptively by visit and analyte.

The potential effects of steady-state administration of osimertinib on the single-dose PK profile of G1T38 will be assessed by ANOVA on the ln-transformed AUC_{inf} and C_{max}. The ANOVA will include treatment as a fixed effect, and subject as a random effect. Each ANOVA included calculation of least squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference. The osimertinib DDI will be assessed using G1T38 plus osimertinib (Test) versus G1T38 alone (Reference). The 90% CIs for the ratios will be derived by exponentiation of the CIs obtained for the difference and the CIs will be expressed as a percentage of Test relative to the Reference.

[redacted]

[redacted]

13. QUALITY CONTROL AND QUALITY ASSURANCE

An eCRF must be completed for each patient enrolled. Once a patient is no longer on the study and the eCRF is completed, the principal investigator will be required to review and sign the eCRF for that patient. The investigator shall 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.

14. ETHICS AND PROTECTION OF HUMAN PATIENTS

14.1. 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 Code of Federal Regulations (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.

14.2. Independent Ethics Committee/Institutional Review Board

The protocol and all associated amendments and consent/assent materials will be reviewed and approved by the investigative site's local IEC/IRB or a central IEC/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 IEC/IRB prior to initiating the study. Approval must be obtained in writing via a letter identifying the protocol, the date of the IEC/IRB meeting, and the date of approval.

14.3. 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.

14.4. 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, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

14.5. 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 protocol will be provided to the IEC/IRB and appropriate local regulatory authorities for approval.

Any protocol amendments will be done in accordance with the provisions agreed upon in Section 14.6. 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.

14.6. Protocol Amendments

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

14.7. Patient Compliance

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

15. DATA HANDLING AND RECORD KEEPING

15.1. 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 drug 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.

15.2. Investigator Reporting Requirements

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

15.3. 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, IEC/IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents may include (but not limited to) patient hospital records, physician's and nurse's notes, original laboratory reports, ECG, electroencephalogram, 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 or longer as required by applicable regulatory authorities.

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.

15.4. 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.

15.5. 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.

16. 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 study.

17. REFERENCES

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Prescribing information: Abemaciclib (Verzenio®)
http://uspl.lilly.com/verzenio/verzenio.html#pi

Prescribing information: Osimertinib (Tagrisso®)
https://www.azpicentral.com/tagrisso/tagrisso.pdf#page=1

Prescribing information: Palbociclib (IBRANCE®)
http://labeling.pfizer.com/ShowLabeling.aspx?id=2191

Prescribing information: Ribociclib (KISQALI®)
https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali.pdf

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18. 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: Prescribing Information for Osimertinib

Tagrisso® (osimertinib) PI, March 2017 link:
https://www.azpicentral.com/tagrisso/tagrisso.pdf#page=1

APPENDIX 3: Drugs that May Prolong the QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.

Drugs Known to Prolong the QT Interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods following cessation of treatment with these agents are provided in Table 18-1.

Table 18-1 Drugs Known to Prolong the QT Interval

Contraindicated Drug	Withdrawal Period Prior to Initiating Osimertinib
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks[a]
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

a Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

Drugs that May Possible Prolong the QT Interval

Use of the drugs in Table 18-2 is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 18-2 Drugs that May Prolong QT Interval

Drug	Minimum Treatment Period on Drug Prior to Initiating Osimertinib
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

APPENDIX 4: Drugs Known to Interact with the P-glycoprotein, BCRP, MATE1, MATE2-K, and OCT1 and 2 Membrane Transporters

The following lists of drugs known to interact with membrane transporters is a representative sample of potentially G1T38-interacting drugs. Caution should be exercised if any of these drugs are concurrently used with G1T38. Use of strong inhibitors of BCRP is prohibited.

Strong Inhibitors of P-gp (use with caution):

- Cyclosporine
- Elacridar
- Ketoconazole
- Reserpine
- Ritonavir
- Tacrolimus
- Valspodar
- Verapamil
- Zouquidar
- Amiodarone
- Carvedilol
- Clarithromycin
- Dronedarone
- Itraconazole
- Lapatinib
- Propafenone

- Quinidine
- Ranolazine
- Telaprevir

Strong Inhibitors of BCRP (use prohibited):

- Elacridar
- Fumitremorgin C
- Ko134
- Ko143
- Novobiocin
- Sulfasalazine
- Curcumin
- Cyclosporine A
- Eltrombopag

Strong Inducers of P-gp (use with caution):

- Carbamazepine
- Phenytoin
- Rifampin
- St. John's Wort
- Tipranavir

MATE1 and MATE2-K Substrates (use with caution):

- Metformin
- MPP+
- Tetraethylammonium (TEA)
- Dofetilide

OCT1 and OCT2 Substrates (use with caution):

- OCT1: metformin, oxaliplatin, aciclovir, ganciclovir
- OCT2: metformin, pindolol, procainamide, ranitidine, amantadine, amiloride, oxaliplatin, varenicline, cisplastin, debrisoquine, proplanolol, guanidine, D-tubocurarine, pancuronium

P-gp Substrates (use with caution):

- Digoxin
- Fexofenadine
- Loperamide
- Quinidine
- Talinolol
- Vinblastine
- Dabigatran

BCRP Substrates (use with caution):

- 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)
- Coumestrol
- Daidzein
- Dantrolene
- Estrone-3-sulfate
- Genistein
- Prazosin
- Sulfasalazine
- Rosuvastatin

APPENDIX 5: RECIST Version 1.1 Time Point Response Evaluation Guidelines for Patients with Nontarget Disease Only

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

CR = complete response; NE = not evaluable; PD = progressive disease

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

Source: Table modified from 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.

APPENDIX 6: Radiotherapy Guidance for Symptomatic Lesions

- Palliative radiotherapy to control symptoms (including gamma knife technique), eg to control brain disease, is permitted.
- For brain and thoracic radiotherapy (only to control symptoms), a 7- to 10-day study drug washout period before the procedure and 1 week period after the procedure before restarting study drug(s) is advised.
- All radiotherapy related toxicities should be managed and ideally resolved before restarting study drug(s).
- Investigators should consider the radiotherapy when assessing causality if there are any localized AEs following the procedure.
- If any lesions (including brain or thoracic disease) are **asymptomatic,** then radiation would not be permitted.