STATISTICAL ANALYSIS PLAN

Study 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)
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Name of Test Drug:	G1T38 (Lerociclib)
Protocol Number:	G1T38-03
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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic chemical
BICR	blinded independent central review
BOR	best overall response
CBR	clinical benefit rate
cfDNA	cell-free DNA
CI	confidence interval
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FAS	full analysis set
HR	hazard ratio
IDMC	independent data monitoring committee
IMP	investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
NTL	nontarget lesion
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival

Abbreviation	Term
PK	pharmacokinetic(s) or PK analysis set, per context
PP	per protocol
PR	partial response
PT	preferred term
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response evaluable analysis set
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMC	safety monitoring committee
SOC	system organ class
StD	standard deviation
TEAE	treatment-emergent adverse event
TL	target lesion
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the detailed analysis and reporting, including tables, listings, and figures, for G1T38-03 ("38-03"), the study of G1T38 in combination with Osimertinib in patients with EGFR mutation-positive metastatic non-small cell lung cancer (NSCLC). The analyses specified in this SAP will be used to support the clinical study report (CSR).

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings to accompany this SAP are specified in a Tables, Figures, and Listings (TLF) shells. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any significant change from the planned analysis in this SAP to provide results for inclusion in the CSR, will be clearly documented in the CSR.

This version of the SAP is based on the protocol version 4.0 dated 02 September 2019. Although the protocol includes study Part 1 and Part 2, Part 2 will not be conducted due to a corporate strategy shift. This SAP describes the analyses of the data collected from Part 1 only.

2. STUDY DESIGN OVERVIEW (PART 1)

This section provides high level information of the study design. Unless as documented in Section 7 (Change From the Protocol), any discrepancies between the protocol language and the text in this section are inadvertent and should not be interpreted as a change to the protocol design.

2.1. Study Objectives

Primary Objective

The primary objectives of Part 1 (Phase 1b) of the study are to:

- Evaluate dose-limiting toxicities (DLTs) associated with G1T38 administered with osimertinib
- Determine the recommended Phase 2 dose (RP2D) of G1T38 administered with osimertinib
- Evaluate the safety and tolerability of G1T38 administered with osimertinib

Secondary Objectives

The secondary objectives of the study are to:

- Assess PFS using investigator assessments (RECIST v1.1)
- Assess response rate and disease control rate (DCR) based on RECIST v1.1 (investigator assessed)
- Assess overall survival (OS)

- Assess 1-year PFS (investigator assessed)
- Assess the effect of osimertinib on pharmacokinetic (PK) parameters of G1T38

Refer to protocol Section 5 for other study objectives and endpoints.

2.2. Study Design

Study 38-03 is an open-label study evaluating 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 RP2D. The study includes 3 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.

Six patients will be enrolled in the first cohort to assess the potential effect of osimertinib on the PK parameters of G1T38. Projected dose levels are presented in Table 6-1 of the Protocol. 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.

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.

Patients will be observed for a DLT during the first cycle of treatment (Cycle 1 Day -16 through Cycle 1 Day 28). Please refer to protocol sections 6.1.1.1. for more information regarding the dose escalation plan as it relates to DLT findings.

2.3. Number of Patients

For Part 1, six patients will be enrolled in the first cohort and additional cohorts may be enrolled using a standard 3 + 3 design with a maximum of 36 patients. The actual number of patients will depend on the number of dose levels/cohorts that are tested.

3. ANALYSIS POPULATIONS (PART 1)

3.1 Definition of Analysis Populations

3.1.1. All Screened Patients

The all screened patients set includes all subjects who consented to participate in the study and completed any screening assessments.

3.1.2. All Enrolled Patients

Enrolled patients are those who consented to participate in the study and have met entry criteria.

3.1.3. Safety Population

The safety population will include all enrolled patients who were administered at least 1 dose of study drug (G1T38 or osimertinib). All safety analyses will be assessed using the safety population. Analyses using the safety population will be conducted on the basis of the actual treatment received.

3.1.4. Response Evaluable Analysis Set (RES)

The response evaluable analysis set (RES) will include all patients who are in the safety population and who have at least one measurable tumor lesion (target lesion(s)) at the baseline tumor assessment, and either (i) have at least one post-baseline tumor assessment, or (ii) do not have post-baseline tumor assessment but have clinical progression as noted by the investigator, or (iii) have died due to disease progression before their first post-baseline tumor scan. The RES will be used for analyses of tumor response.

3.1.5. Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all enrolled patients who were administered at least one dose of continuous daily of G1T38 (i.e., Cycle 1 Day 1). All analyses using FAS will be conducted by the dose level cohort that was assigned at enrollment. The FAS is the primary analysis set for efficacy analyses, unless otherwise specified.

4. PRIMARY AND SECONDARY ENDPOINTS

For safety endpoints, baseline is defined as the last non-missing value prior to or on the date/time of first administration of investigational medicinal product (IMP) (G1T38 or osimertinib) during the PK period (i.e., Cycle 1 Day -16 for G1T38, or Cycle 1 Day -14 for osimertinib). If the latest pre-dose value is collected on the day of treatment, the time of treatment if available will be used to identify the baseline value. Change from baseline to post-baseline will be calculated as post-baseline value minus the baseline value. Change from baseline is calculated only when both post baseline value and baseline value are non-missing. For efficacy endpoints, the last non-missing value prior to or on the date/time of first administration of daily (i.e., continuous) dosing of the IMP (i.e., Cycle 1 Day 1) will be used as baseline.

4.1 Efficacy Endpoints

4.1.1 General Consideration for Tumor Response Assessment

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

The methods used at baseline (i.e., the screening visit) for assessment of tumor burden (computed tomography [CT] or magnetic resonance imaging [MRI] scans of chest and abdomen [including liver and adrenal glands]) must be used at each subsequent follow-up assessment. 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 every 8 weeks relative to Cycle 1 Day 1 until the date of (i) radiographic disease progression as defined by RECIST 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent to obtain scans; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. After 18 months of treatment, subsequent tumor assessments shall be performed every 12 weeks (± 1 week).

At each tumor assessment visit, an overall visit response by RECIST will be determined programmatically - using the information from investigator's measurement of target lesions (TL), non-target lesions (NTLs) and new lesions collected on electronic case report form (eCRF). The overall response at each time point is also assessed by the investigators and is collected on eCRF.

Antitumor efficacy endpoints include the following based on RECIST v1.1

- Best Overall Response (BOR)
- Objective response rate (ORR) (complete response [CR] or partial response [PR])
- Duration of objective response (DOR), and time to first objective response
- DCR at week 8 (complete response [CR] or partial response [PR] or stable disease [SD])
- PFS

4.1.2 Definitions of Efficacy Endpoints

4.1.2.1 Tumor Responses

Target lesions (TLs)

Measurable disease at baseline is defined as having at least one measurable lesion which is

- ≥10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥15 mm) with CT or MRI; or
- ≥10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); or for lymph nodes which must have short axis ≥15 mm by clinical exam; or
- ≥ 20 mm by chest X-ray.

In rare cases, lesions measured by methods other than CR, MRI, caliper, or X-ray should be discussed with G1 medical team to determine if the lesions should be counted as measurable disease.

A tumor lesion that has been previously irradiated may be considered measurable if unequivocal growth of the lesion has been demonstrated. A patient can have a maximum of 5 measurable lesions representative of all involved organs (maximum of 2 lesions per organ, both the lymph node and skin will be considered as a single organ) recorded at baseline and these are referred to as target lesions. If more than one baseline scan (prior to or on Cycle 1 Day 1) is recorded, then measurements from the scan that is closest to Cycle 1 Day 1 will be used to define the baseline sum of TLs.

Table 1 gives definition of TL visit responses.

Table 1 Definition of TL visit responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions 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 as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5mm, taking as reference the smallest sum on study (i.e. nadir) since treatment started including the baseline sum if that is the smallest on study.
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.
Not Evaluable (NE)	Any target lesion measurements are missing and PD status could not be determined based on lesions with non-missing measurements.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a target lesion response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

If any target lesion measurements are missing, then the target lesion visit response is Not Evaluable (NE), unless a convincing argument can be made that the contribution of the individual missing lesions(s) would not change the assigned time point response. The overall visit response will also be NE, unless there is a progression of non-target lesions or new lesions, in which case the response will be PD.

TL too small to measure

If a target lesion becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured.

Lesions that split

If a TL splits, then the LDs of the split lesions should be summed up and reported as the LD for the lesion that split.

Lesions that merge

If target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0mm.

Modality change

The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. In case of modality changes, for programmatically derived response, each case should be discussed with medical team to determine if data from substituted approaches should be used, if not, the patient should be considered not evaluable from that point forward. However, a response from the investigator that differs from the programmatically derived response is acceptable if a definitive response assessment can be justified based on the available information.

Non-Target Lesions (NTLs)

All other lesions, including measurable lesions that are not selected as target lesions and all small lesions that do not meet the measurable disease criteria.

The non-target lesion response will be based on the derived timepoint response assessment(s) of NTLs as defined in Table 2:

Table 2 Definition of NTLs visit responses

Visit Responses	Description
CR	Disappearance of all NTLs. All lymph nodes must be < 10 mm short axis.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
PD	Unequivocal progression of existing NTLs. Unequivocal progression is defined as, "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 one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status

NE	Only relevant when one or some of the NTLs have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment.

New lesions

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

Time Point Response (TPR)

Table 3-1 defines how the previously defined TL and NTL responses will be combined with new lesion information to give an overall response at each time point. The possible overall responses at a visit are CR, PR, SD, PD, and NE.

Table 3-1 Evaluation of Overall Response at Each Time Point – patients with target lesion(s)

Target Lesions	Non-target 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 all evaluated	No	PR
SD	Non-PD/not all 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 et al, 2009)

For patients without any target lesion, Table 3-2 defines how the previously defined NTL responses will be combined with new lesion information to give an overall response at each time point. The possible overall responses at a visit are CR, Non-CR/Non-PD, PD, and NE.

Table 3-2 Evaluation of Overall Response at Each Time Point – patients without target lesion(s)		
Non-target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, NE = not evaluable
Source: (Eisenhauer et al, 2009)

At each tumor assessment visit, an overall time point response of CR, PR, SD, Non-CR/Non-PD, PD or NE by RECIST Version 1.1 will be determined programmatically, using the information from TL, NTLs, and new lesions.

Best Overall Response

Best overall response is defined as the best overall response across all time points. BOR will be determined using overall time point responses up until the last evaluable time point response prior to or on the date of (i) radiographic disease progression as defined by RECIST 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

A patient's BOR will be determined based on Table 4. For data-driven scenarios which may not be covered by Table 4, the BOR will be reviewed and determined by the medical advisors and statisticians prior to database lock.

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 (i.e., it will not include the response after the patient has progressed).

According to tumor assessment schedule (Table 9-1 in protocol), the first post-baseline disease assessment will be obtained at the end of Cycle 2 (study day 56) with a window ±7 days (study day 49 through day 63). Therefore, a patient will be considered to have BOR of SD or Non-CR/Non-PD if a SD or Non-CR/Non-PD time point response is recorded no earlier than Day 49 since first G1T38 daily continuous dosing (Cycle 1 Day 1).

When the minimum interval (i.e., 4 weeks) for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR for a patient, then two ways of assigning BOR will be implemented in the analysis (Table 4). In the primary analysis, BOR will be assigned as stable disease (SD) according to RECIST 1.1, provided minimum 49 days SD duration criteria met, otherwise BOR will be assigned as PD or NE depends on the response of the confirmation assessment.in the other method, two more response categories will be added as unconfirmed CR and unconfirmed PR.

Table 4 Best Overall Response When Confirmation of CR and PR are Required [a]

First TPR[b]	Subsequent TPR	Best overall response (confirmed CR and PR)	Best Overall Response*(Confirmed and unconfirmed CR and PR)
CR	CR	CR	CR
CR	PR	SD [c] or PD	Unconfirmed CR
CR	SD or Non-CR/Non-PD	SD or Non-CR/Non-PD [c] or PD	Unconfirmed CR
CR	PD	SD or Non-CR/Non-PD [c] or PD	Unconfirmed CR
CR	NE or NA	SD or Non-CR/Non-PD[d] or NE	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD	Unconfirmed PR
PR	PD	SD [c]or PD	Unconfirmed PR
PR	NE or NA	SD [d] or NE	Unconfirmed PR
NE	NE	NE	NE

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not available; ORR = Objective Response Rate, TPR = time point response.

a. The minimum interval for confirmation of CR and PR is 4 weeks (28 days).

b. First appearance of CR or PR per RECIST 1.1.

c. Best response will be SD or Non-CR/Non-PD if the first time point overall response is on or after 49 days on study. Otherwise, the best response will be PD.

d. Best response will be SD or Non-CR/Non-PD if the first time point overall response is on or after 49 days on study. Otherwise, the best response will be NE.

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A best overall response of SD or Non-CR/Non-PD can only be made after the patient has tumor assessment on day 49 (counted from first once-daily dosing date, Cycle 1 Day 1) or later. Otherwise, any tumor assessment indicated stable disease before this time period will have a best response of NE unless PD is identified. If a PD is indicated for the first TPR, then the BOR will be PD regardless of subsequent TPRs.

Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening not evaluable (NE) (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmed PR.

Objective Response Rate

Objective response rate will be calculated based on either (1) confirmed tumor responses or (2) confirmed and unconfirmed tumor responses

Objective response will be derived as No/Yes (0/1) variable. For confirmed objective response ($OR_{CONFIRMED}$), 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, ORR is defined as the proportion of patients with confirmed objective response being "Yes"among the analysis set.

Unconfirmed objective response ($OR_{UNCONFIRMED}$) will be derived as No/Yes (0/1) variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with $OR_{UNCONFIRMED}$ being "Yes".

Disease Control Rate at Week 8

Disease control rate (DCR) at Week 8 is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR or SD or Non-CR/Non-PD at 8 weeks. For patients without measurable lesions at baseline, a BOR of Non-CR/Non-PD will be considered achieving disease control.

Duration of Objective Response

Duration of objective response (DOR) is the time between first objective response of CR or PR and the first date that progressive disease (PD) is objectively documented or death. Patients who experienced an objective response but who do not experience objective PD or death at the time of analysis will be censored at the last adequate assessment date. Adequate assessment is defined as there is sufficient data to evaluate a patient's disease status. DOR will be calculated only for patients who experience a confirmed objective response.

Time to First Objective Response

Time to first objective response is the time from first dose of once-daily dosing of G1T38 (Cycle 1 Day 1) to first objective response of CR or PR. This variable will be calculated only for patients who experience a confirmed objective response.

Progression-free Survival

Progressive disease (PD) is defined as radiographical determined disease progression based on the criteria by RECIST Version 1.1, which is also referred to as "documented disease progression" in the SAP. PD status is derived from the radiographical assessments by investigators that have been entered to the EDC. A PFS event is defined as a PD event or a death due to any cause.

PFS is defined as the time (months) from start date of continuous daily of G1T38 (i.e. Cycle 1 Day 1) to the date of the first documented PFS event, and the time from start date of continuous daily of G1T38 to the censoring date for those patients that did not experience a PFS event. That is, PFS is calculated as (date of PFS event or censoring – start date of continuous daily of G1T38 + 1)/

30.4375. In general the date of PD will be determined using all radiographical assessment data up until the last adequate visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1, (ii) withdrawal of consent, or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. The "adequate visit" is defined as the visit when all scheduled tumor assessments have been performed. Specifically, if PD and new anti-cancer therapy occurred on the same day for a patient, it is assumed that the PD occurred first.

The primary PFS analysis is to assess PFS before treatment discontinuation. PFS will also be evaluated including tumor assessment data post the last dose of study drug (denoted as the secondary PFS analysis). The censoring rules for the primary PFS analysis are provided in Table 5-1, while the censoring rules for the secondary PFS analysis are presented in Table 5-2.

Table 5-1 PFS Calculation and Censoring Rules for the Primary PFS Analysis

Situation	Date of PD Event or Censored	Outcome
Incomplete or no baseline tumor assessments	Date of Cycle 1 Day 1	Censored
No progression	Date of the last adequate radiological disease assessment with no documented disease progression	Censored
Treatment discontinuation for reasons other than disease progression	Date of the last adequate radiological disease assessment with no documented progression	Censored
New anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment no later than the initiation of new anticancer treatment	Censored
Disease progression per RECIST Version 1.1	Date of the first documented progression	PFS event
Death in the absence of documented PD	Date of death	PFS event

Table 5-2 PFS Calculation and Censoring Rules for the Secondary PFS Analysis

Situation	Date of PD Event or Censored	Outcome
Incomplete or no baseline tumor assessments	Date of Cycle 1 Day 1	Censored
No progression	Date of the last adequate radiological disease assessment with no documented disease progression	Censored

Treatment discontinuation for reasons other than disease progression, and disease progression documented post last dose of study drug	Date of the last adequate radiological disease assessment	PFS event
Treatment discontinuation for reasons other than disease progression, and no disease progression documented post last dose of study drug	Date of the last adequate radiological disease assessment	Censored
New anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment no later than the initiation of new anticancer treatment	Censored
Disease progression per RECIST Version 1.1	Date of the first documented progression	PFS event
Death without a PD	Date of death	PFS event

4.2. Safety Endpoints

The safety variables include:

4.2.1. Adverse Events (AEs)

The severity (toxicity grade) of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

Treatment-emergent AEs (TEAEs) are defined as any AE occurring on or after the first dose of study drug (i.e., C1D-16) until 30 days after the last dose of study drug (G1T38 or Osimertinib, which is later) but prior to the start of survival follow-up. For AEs with an incomplete or unknown/not reported onset date, the imputed onset date will be used to determine if the AE is treatment-emergent.

AEs with onset dates that are partially/completely missing will be imputed as follows:

If the start date has month and year but day is missing,

- If the month and year is the same as the first dose date, then the first dose date will be used, otherwise, the first day of the month will be used

If the start date has year, but day and month are missing,

- If the year is the same as the first dose date, then the first dose date will be used, otherwise 1st Jan will be used

If the start date of an event is completely missing, then AE start date is imputed with the first dose date.

After imputation, the imputed start date will be compared with the complete or imputed (if missing or partial) AE stop date. If the imputed start date is later than the stop date, the stop date will be used as imputed start date instead.

Imputation rules for missing or partial AE stop date are defined below:

- If the stop date has month and year but day is missing, the last day of the month will be imputed
- If the stop date has year, but day and month are missing, the 31st of December will be imputed
- If the AE end date is completely missing, the last dose date +30 days will be used as the AE end date.

  After the imputation, the imputed AE stop dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

The following durations will be derived for an AE, AE leading to death, AE leading to discontinuation of any study drug as appropriate and will be displayed in the corresponding AE listings. Cycle 1 Day -16 is used for date of first dose.

- Relative study day for the onset of AE: (AE onset date – date of first dose + 1) if AE onset date is on or after the date of first dose; otherwise (AE onset date – date of first dose)
- Relative study day for the end of AE: (AE stop date – date of first dose + 1) if AE stop date is on or after the date of first dose; otherwise (AE stop date – date of first dose)
- The duration of AE: AE stop date – AE onset date + 1

Drug related AEs are defined as related if causality is related.

Every attempt will be made to obtain complete information for AEs regarding severity (i.e., CTCAE Grade) and relationship to drug; however, in the rare case of missing data, the following conservative approach will be taken for summary purpose. The non-imputed raw data will be presented in AE listings,

- Missing AE grade will be classified as ‘Grade 3’
- Missing AE relationship will be classified as “Related”

AEs related to hematological toxicity is of significant clinical interest, Certain PTs will be consolidated into larger categories outside the traditional MedDRA coding guidance. Table 6-1 outlines those terms that will be consolidated.

Table 6-1 Hematologic Preferred Terms to be Consolidated

Presented SOC/PTs in the table	Dictionary SOC/PT
Blood and lymphatic system disorders / Neutropenia	Blood and lymphatic system disorders / Neutropenia
	Investigations / Neutrophil count decreased
Blood and lymphatic system disorders / Anemia	Blood and lymphatic system disorders / Anemia
	Blood and lymphatic system disorders / Anaemia
	Investigations / Red blood cell count decreased
	Investigations / Hemoglobin decreased
Blood and lymphatic system disorders / Thrombocytopenia	Blood and lymphatic system disorders / Thrombocytopenia
	Investigations / Platelet count decreased
Blood and lymphatic system disorders / Lymphocytopenia	Blood and lymphatic system disorders / Lymphocytopenia
	Blood and lymphatic system disorders / Lymphopenia
	Investigations / Lymphocyte count decreased
Blood and lymphatic system disorders / Leukopenia	Blood and lymphatic system disorders / Leukopenia
	Investigations / White blood cell count decreased

In addition, the following gastrointestinal PTs are collapsed in Table 6-2.

Table 6-2 Gastrointestinal Preferred Terms to be Consolidated

Presented term in the table	Preferred Term
Stomatitis	Mouth ulcers
	Mouth ulceration
	Mucosal inflammation
	Stomatitis
	Aphthous stomatitis

4.2.2. Dose-Limiting Toxicities (DLTs)

DLTs will be evaluated from Cycle 1 Day -16 through Cycle 1 Day 28 (the DLT period). DLTs 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).

4.2.3. Vital Signs

Vital signs include weight, temperature, systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse rate, and respiration rate.

Vital sign potentially clinically significant criteria are defined in the Table 7 below:

Table 7 Vital Sign Potentially Clinically Significant Criteria

Vital Sign Parameter	Criterion value	Change from baseline
SBP	≥180 mmHg ≤ 90 mmHg	Increase ≥30 mmHg Decrease ≥20 mmHg
DBP	≥105 mmHg ≤ 50 mmHg	Increase ≥20 mmHg Decrease ≥10 mmHg
Pulse	≥ 120 bpm ≤ 50 bpm	Increase ≥20 bpm Decrease ≥20 bpm
Weight	n/a	Change ≥15%

bpm = beats per minute

4.2.4. Laboratory

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be collected. The laboratory variables in Table 8 will be measured.

Laboratory toxicities will be assessed using the NCI CTCAE, Version 4.03. Details on CTCAE grading criteria are presented in the Appendix Table A1. Change from baseline and percent change from baseline in laboratory test results to each assessment will also be derived.

Table 8 Clinical Laboratory Tests

Hematology	**Chemistry**
Hemoglobin Hematocrit WBCs with differential Platelets	Albumin Alkaline phosphatase Total bilirubin Calcium Chloride Creatinine Glucose 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 it is available as a local test

Collected serum calcium will not be summarized in tables, instead, corrected serum calcium will be derived from calcium and albumin results based on the following formula:

Corrected Calcium = Calcium (mmol/L) + 0.02 (40 - [Albumin] (g/L)

Laboratory Values with < or > Inequality Symbols

Some continuous laboratory data include "<" or ">" symbols. Data will be presented in listings with their inequality symbol; however, for tabulation of summary statistics of safety laboratory results, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

4.2.5. Electrocardiograms (ECGs)

All patients will have three 12-lead electrocardiograms (ECGs) performed at the visits indicated in Table 9-1 of the protocol.

Part 1 Triplicate 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)

Collected QTcB and QTcF will not be summarized in tables, but will instead be derived from the QT and Heart Rate (HR) based on the following formulas:

(i) Bazett (obtained in milliseconds): $QTcB = QT/ (RR^{1/2})$

(ii) Fridericia (obtained in milliseconds): $QTcF=QT/(RR^{1/3})$

where QT is measured in milliseconds, RR is derived in seconds from HR in beats-per-minute (bmp):

RR (seconds) = 60/(HR in beats-per-minute).

If QT and/or HR is missing, then QTcB and QTcF will be left as missing.

ECG potentially clinically significant criteria are listed in Table 9 below:

Table 9 ECG Potentially Clinically Significant Criteria

ECG Parameter	Criterion- Observed Value	Criterion-Change from Baseline
Heart Rate	>120 bpm	n/a
	<50 bpm	n/a
PR Interval	≥ 210 ms	n/a
RR Interval	>1200 ms	n/a
	<500 ms	n/a
QRS Interval	≥ 120 ms	n/a
	≤ 50 ms	n/a
QT Interval	≥ 500 ms	n/a
	≤ 300 ms	n/a
QTcB, QTcF Intervals	≥ 500 ms	increase ≥ 30 and < 60 ms
	≥ 480 and < 500 ms	increase ≥ 60 ms
	≥ 450 and < 480 ms	decrease ≥ 30 ms and < 60 ms
	>300 and < 450 ms	decrease ≥ 60 ms
	≤ 300 ms	
The average value is used for the criteria if multiple assessments are planned at a nominal timepoint		

4.2.6. Echocardiogram/MUGA

An echocardiogram/ multigated acquisition (MUGA) scan to assess LVEF (left ventricular ejection fraction) shall be performed at the time points outlined in Table 9-1 of the protocol.

4.2.7. Treatment Exposure and Compliance

Prescribed duration of treatment (days) is defined as the total number of days that the patient will have been prescribed study medication, that is, including days on treatment before Cycle 1 Day 1 and days on treatment from Cycle 1 Day 1 to treatment end day. Prescribed duration of G1T38 (months) is calculated as (last dose date on the dosing log – first date of continuous daily dosing (C1D1) + x + 1)/30.4375, where x is the number of days patient received G1T38 before C1D1. For example, for a patient who took one dose of G1T38 each on C1D-16 and C1D-2 respectively and took last dose on or after the first date of continuous, daily dosing of G1T38 (C1D1), Days on Treatment = Date of last dose – C1D1 date + 3; for patients who did not start continuous daily dosing, total number of days on dosing of G1T38 before C1D1 will be used as prescribed duration. Prescribed duration of Osimertinib (months) is calculated as (last dose date on the dosing log - the first date of daily osimertinib (only) dosing (i.e., C1D-14) + 1)/30.4375.

The exposure to G1T38 (months) is calculated by (prescribed G1T38 duration - days of interruption as captured in dosing log)/30.4375. Days of interruption is defined as (start date of next record – end date of current record – 1).

For subjects with last dose date is missing from dosing log, if end of treatment date is not missing, date of end of treatment will be used as last dose date. Otherwise, the later date between the last visit date during the treatment phase and last contact date will be used, but the date must be prior to the start of survival follow-up.

Compliance of G1T38 is expressed as a percentage of days G1T38 was actually taken during the treatment phase and will be calculated as exposure to G1T38 divided by prescribed G1T38 duration multiplied by 100.

Dose reduction will be flagged when a total daily dose recorded in G1T38 dosing log is less than the previous entry. Patient with dose interval change but total daily dose unchanged (e.g. 300 mg QD vs 150 mg BID) will not be considered as dose reduction.

5. ANALYSIS METHODS (PART 1)

5.1 General Principles

5.1.1. General Statistical Considerations

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

Data will be summarized descriptively by dose level and overall.

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 (SD), and minimum and maximum values. The descriptive summary statistics of time to first objective response will include median, 25% and 75% percentiles, and minimum and maximum values. The Kaplan-Meier method will be used to estimate the probability of survival (PFS and DOR) and the respective the time-to-event percentiles.

In general, the precision of descriptive statistics for continues variables min and max will always be consistent with the precision of the variable of summarization. Additional rounding rules are listed as follows:

- If the original value has <= 1 decimal places, mean and median will have one more decimal as the original value. Measures of variability (e.g, SD will be rounded two more decimal places than the precision of the original measure.
- If the original value has two decimal places, mean and median will have the same decimal places as the original value. Measures of variability will be rounded one more decimal place than the precision of the original measure.
- If the original value has >2 decimal places, all the descriptive statistics will have the same decimal places as the original value.

For categorical variables, non-zero percentages will be displayed with 1 decimal place, zero-percentages will not be displayed. A percentage value less than 0.1% will be displayed as "<0.1%." A percentage value less than 100% but greater than 99% will be displayed as ">99%."

Part 1 of the study is descriptive in nature. No formal statistical test will be conducted. Two-sided 95% exact CI will be provided for tumor response rate by using Clopper-Pearson method. 95% CI will be provided for PFS percentiles by using log-log transformation approach.

Any rounding will be done after all calculations are made.

Safety assessments (other than AEs) during treatment period is defined as assessment that is evaluated between the date of first dose of study drug and the date of last dose of study drug + *29* days. Assessments occur on or after last dose of study drug + 30 days will be counted as assessments during post-treatment period. If start date of survival follow up is available, assessments during post-treatment period should occur prior to the start of survival. If the last dose date of study drug is missing, any assessment/event occurring after the start of study drug will be considered as during treatment period.

All data will be listed for all enrolled patients.

5.1.2. Handling of Missing Data

All data will be analyzed as they were collected in the database. In general, missing data, unless noted otherwise, will not be imputed. However, imputation of missing AE (Section 4.2.1) and concomitant medication (Section 5.2.6) onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using available data. For continuous variables, subjects with missing data will be excluded from analyses for which data are not available. For categorical variables, a "Missing" category will be added for subjects with missing data.

5.1.3. Study Days and Visit Windowing

Study Days Relative to First Administration of Study Medication on Cycle 1 Day 1

Study Day 1 is the day continuous daily doses of G1T38 and osimertinib commences.

Negative Study Days occur prior to first administration of study medication on C1D1; and positive Study Days are those after the first administration of study medication on C1D1– e.g., Study Day -1 is the day immediately preceding the first administration of study medication on C1D1, Study Day 2 is the day immediately following the first administration of study medication on C1D1.

Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug on C1D1 – defined as Day 1 – to the dates that the scheduled visit occurs. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days. The visit-window mapping is described in Table 10 for Part 1 for safety assessments. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in by patient listings.

For windowed visit between the treatment start date (i.e., Cycle 1 Day -16) through post-treatment visit, if more than one visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit.

For a patient who prematurely discontinues treatment, the visit will be slotted accordingly. The window for post-treatment visit will be from the "last dose date + 30 to date of last assessment prior to the start of survival follow-up".

Table 10 Windowing Algorithm for Part 1

Visit	Scheduled Day	Vital Signs	Clinical Chemistry	Hematology	Urinalysis and ECOG	ECG
Screening	NA	-37 to -17	-37 to -17	-37 to -17	-37 to -17	-37 to -17
C1D-16	-16	-16	-16	-16	-16	-16
C1D-2	-2	-15 to -1				-15 to -1
C1D1	1	1 to 3	-15 to 3	-15 to 3	-15 to 3	
C1D8	8			4 to 11		
C1D15	15	4 to 21	4 to 21	12 to 18		
C1D22	22			19 to 25		
C2D1	29	22 to 35	22 to 35	26 to 32	4 to 42	1 to 42

C2D8	36			33 to 39		
C2D15	43	36 to 49	36 to 49	40 to 46		
C2D22	50			47 to 53		
C3D1	57	50 to 70	50 to 63	54 to 63	43 to 70	43 to 70
C3D15	71		64 to 77	64 to 77		
C4D1	85	71 to 98	78 to 91	78 to 91	71 to 98	
C4D15	99		92 to 105	92 to 105		
C5D1	113	99 to 126	106 to 126	106 to 126	99 to 126	
CYD1[a]	28(Y-1)+1	28(Y-1)-13 to 28(Y-1)+14	28(Y-1)-13 to 28(Y-1)+14	28(Y-1)-6 to 28(Y-1)+7	28(Y-1)-13 to 28(Y-1)+14	28(Y-1)-13 to 28(Y-1)+14
CYD15[a]	28(Y-1)+15			28(Y-1)+8 to 28(Y-1)+21		
Post-treatment visit	Last dose date + 30 days					

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.

5.2 Analysis Methods (Part 1)

5.2.1. Patient Disposition

- The number of patients in following categories will be summarized for all screened patients without percentages, only for the overall treatment:
  - Screened patients
  - Screen failures and reasons for screen failure
- The number of patients and percentages will be summarized for all screened patients by treatment for:
  - Enrolled patients
- The number of patients and percentages in the following categories will be summarized based on the safety population by treatment group and overall, unless otherwise specified:
  - Patients treated (safety population)
  - Patients not treated

- Full analysis Set
- Response evaluable analysis set
- Treatment disposition along with reason for discontinuation
- Continued with study survival follow-up at end of treatment
- Study disposition along with the reasons for discontinuation
- Death summary (death and reasons)

Listings will be provided for enrollment information (country, date of protocol version, date of informed consent, and date of first dose), end of treatment disposition, end of study disposition and death.

5.2.2. Protocol Deviations

Protocol deviations will be classified as major or minor for severity based on if they may affect the ability to assess the safety and efficacy of study drug. The classification of protocol deviations will be finalized at the Classification Meeting prior to database lock.

The number and percentage of patients by dose level and overall and deviation type will be presented for all major protocol deviations for safety population. All protocol deviations will be listed including detailed description, deviation type and subtype and classification for major or minor based on data recorded on Protocol Deviation Logs, including unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures, provided by PAREXEL Medical.

5.2.3. Demographic and Other Baseline Characteristics

Demographics – age (at informed consent), sex, child-bearing potential (female patients only), race, ethnicity – and baseline patient characteristics including height (cm), weight (kg), BMI (kg/m^2), and smoking history (history of smoking – Y/N, average packs per day, and years smoking) will be tabulated by dose level and overall, using all patients in the safety population to descriptively assess the comparability of the groups. Body mass index (BMI) (kg/m^2) is calculated by weight (kg)/[height (m)]^2.

The following baseline lung cancer characteristics will be summarized as continuous or categorical variables, where appropriate:

- Tumor type at initial diagnosis
- Stage of disease at initial diagnosis
- Time from initial diagnosis to first dose day (in months)
- Current status of brain metastases
- EGFR mutation status and the identified mutations

- Eastern Cooperative Oncology Group (ECOG) performance status

All data will be listed for all enrolled patients.

5.2.4. Prior Cancer Therapy

Patient prior cancer therapy will be tabulated by dose level and overall using all patients in the safety population. This table will include the total number of prior treatments in the advanced/metastatic setting per patient (summarized as both continuous variable and categorical variable (0, 1, 2, 3, and >=4)); the treatment type of prior treatment by treatment setting; time since the last prior systemic anti-cancer therapy; the reason for discontinuation of the last prior systemic anti-cancer therapy; any prior cancer surgery (lung) (yes/no); any radiation treatment (yes/no); the number of patients with prior EGFR TKI treatment (i.e., Osimertinib or Other) and any discontinuation of EGFR TKI treatment due to disease progression. Prior cancer treatments will be listed and are coded according to the World Health Organization (WHO) Drug Dictionary (WHODrug) March 2020 DDE B3.

Time since the Last Prior Systemic Anti-Cancer Therapy (Months) is calculated as (first dosing date for pharmacokinetics assessments (i.e. C1D-16) – date of last prior systemic anti-cancer therapy + 1)/30.4375. If the month and year of the therapy are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1 for the calculation. If the year is missing, the patient will be excluded from the analysis.

5.2.5. Medical History

Medical history will be coded using MedDRA Version 23.0. Medical history will be listed for all enrolled patients (SOC, PT, and verbatim term) by dose level and overall.

5.2.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHODrug version dated March 2020 DDE B3. Prior medications include medications that were taken prior to the first dose of any study treatment. Concomitant medications during the treatment period include medications that started at any time and were taken at any time after the start of study treatment until 29 days after the end of study treatment. Post-treatment medications are those medications were started on or after the last dose of study drug (G1T38 or osimertinib, which is later) + 30 days.

Medications with incomplete start and/or end dates will be imputed for the purpose of classification of prior and concomitant according to the specifications described below. Medications with incomplete start and/or end dates will be assumed to be concomitant if it cannot be shown that the medication was not taken during the treatment period.

Imputation rules for missing or partially missing medication start/stop dates are defined below:

Missing or partially missing medication start date:

If the start date has month and year but day is missing,

- If the month and year is the same as the first dose date, then the first dose date will be used, otherwise, the first day of the month will be used

If the start date has year, but day and month are missing,

- If the year is the same as the first dose date, then the first dose date will be used, otherwise 1st Jan will be used

If the start date of an event is completely missing, then the start date will be imputed as the earlier date between

- the first dose date of study drug
- the end date of the medication (if complete date)

Any above imputed started date should be no later than the end date, if available. In case the imputed started date is later than the end date, the start date will be imputed as the end date of the medication.

Missing or partial medication stop date:

- If the stop date has month and year but day is missing, the last day of the month will be imputed
- If the stop date has year, but day and month are missing, the 31st of December will be imputed
- If the medication is not ongoing, the end date is completely missing, the end date will be imputed as the later date between:
  - the date of last study visit
  - the start date of the medication (if complete date)

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

The number and percentage of patients taking concomitant medications during the treatment period will be summarized by anatomical therapeutic chemical (ATC) class level 4 (chemical subgroup) and PT for the safety population. Although a patient may have taken the same medication multiple times, the patient is counted only once within an ATC classification. The same patient may contribute to two or more PTs in the same classification.

All medications will be listed for enrolled patients with a flag for prior and/or concomitant, or post-treatment.

5.2.7. Treatment Duration

Study drug exposures will be summarized for the safety population using descriptive statistics.

Exposure to G1T38 and Osimertinib will be categorized in intervals (<3 Months, 3 - <6 Months, 6 - <9 Months, 9 - <12 Months, 12 - <15 Months, 15 - <18 Months, 18 - <21 Months, 21 - <24 Months, >=24 Months) and summarized by dose level and overall. Interval in Months is calculated by duration in days/30.4375.

5.2.8 Treatment Compliance

G1T38 drug compliance will be summarized using descriptive statistics. The compliance summaries will include the prescribed G1T38 duration (in months), the exposure to G1T38 (in months), and the proportion (%) of days G1T38 is taken. The proportion (%) of days G1T38 is taken will also be summarized in categories "<70%", "≥70% - <80%", "≥80% - <90%", "≥90% - <100%", and "=100%." The number and percentage of patients with any G1T38 dose reductions will also be summarized.

Study drug compliance summaries will be based on the safety population.

A listing of exposure and compliance data containing the information described in the sections above will be provided.

5.2.9. Efficacy Analyses

5.2.9.1 Analysis of Tumor Response

The number and percentage of subjects in each category of BOR according to programmatically-derived tumor response (CR, PR, SD, PD, or NE) based on investigator's measurements will be presented by dose level and overall. Also, the number and percentage of subjects in each category of BOR (Confirmed CR, Confirmed PR, SD, PD, or NE) based on CRF collected timepoint response (confirmed) will be summarized by dose level and overall. Similar analyses will be repeated for ORR and DCR.

Estimates of response rate, along with its associated exact 95% two-sided CIs using Clopper-Pearson method will be computed for ORR, BOR, and DCR within each treatment group.

The above analyses will be based on the RES. Analysis will be repeated for FAS based on programmatically derived BOR (confirmed) and DCR with additional category of Non-CR/Non-PR.

In addition to confirmed response ($CR_{confirmed}$, $PR_{confirmed}$ and $ORR_{confirmed}$) in BOR summary, both confirmed response and unconfirmed response ($CR_{unconfirmed}$, $PR_{unconfirmed}$, and $ORR_{unconfirmed}$) will be presented in a separated BOR summary based on programmatically derived response for response evaluable population.

Detailed tumor assessment data from CRF will be listed together with derived response for target lesion(s) and derived time point response for all enrolled patients.

5.2.9.2 Analysis of DOR and time to first objective response

Summary of DOR and time to first objective response will be presented for patients with objective response in RES. DOR will be analyzed using Kaplan-Meier analyses. The following

summaries will be presented: a summary of the number of censored and event observation; estimated statistics, including median, 25% and 75% percentiles and associated 95% confidence interval (CI).

Descriptive statistics of median and range will be produced for time to first response based on patients with an objective response in the RES.

5.2.9.3 Analysis of PFS

PFS will be analyzed using Kaplan-Meier analyses based on FAS. The following summaries will be presented: a summary of the number of event and censored observation, along with the censoring reasons; estimated statistics, including median, 25% and 75% percentiles and associated 95% confidence interval (CI). In addition, estimated the probability of survival at pre-specified landmarks (every 6 months from month 6 through month 24) and the 95% confidence interval (CI) will be presented in PFS tables. The estimated probability of PFS over time will be displayed graphically, when appropriate.

All efficacy data will also be listed by patient.

5.2.10. Safety Analyses (Part 1)

Adverse Events

Details for imputing missing or partial start dates of AEs are described in Section 4.2.1.

AE overall summary tables will be presented for TEAEs only and will include the following:

- Number of TEAEs (all events are counted)

And, patients with any,

- TEAEs
- Grade 3 or higher TEAEs
- TEAEs related to either G1T38 or Osimertinib
  - G1T38-related TEAEs
  - Osimertinib-related TEAEs
  - G1T38 and Osimertinib-related TEAEs
- Grade 3 or higher TEAEs related to either G1T38 or Osimertinib
  - Grade 3 or higher G1T38-related TEAEs
  - Grade 3 or higher Osimertinib-related TEAEs
  - Grade 3 or higher G1T38 and Osimertinib-related TEAEs
- Serious TEAEs

- Grade 5 TEAEs or TEAEs with fatal outcome (death)
- Serious TEAEs related to either G1T38 or Osimertinib
  - G1T38-related serious TEAEs
  - Osimertinib-related serious TEAEs
  - G1T38 and Osimertinib-related serious TEAEs
- TEAE leading to G1T38 dose reduction
- TEAEs leading to discontinuation of either G1T38 or osimertinib
  - TEAEs leading to discontinuation of G1T38
  - TEAEs leading to discontinuation of Osimertinib
  - TEAEs leading to discontinuation of G1T38 and Osimertinib

TEAEs will be summarized in descending frequency of all dose levels combined as follows:

- TEAEs by SOC and PT (without collapsed terms);
- Serious TEAEs by SOC and PT;
- TEAEs by PT and by CTCAE grade;
- G1T38-related TEAEs by PT and by CTCAE grade;
- Osimertinib-related TEAEs by PT and by CTCAE grade;
- G1T38-related and Osimertinib-related TEAEs by PT and by CTCAE grade;
- G1T38-related or Osimertinib-related TEAEs by PT and by CTCAE grade;
- G1T38-related TEAEs by SOC and PT;
- Osimertinib-related TEAEs by SOC and PT;
- G1T38-related and Osimertinib-related TEAEs by SOC and PT;
- G1T38-related or Osimertinib-related TEAEs by SOC and PT;
- G1T38-related serious TEAEs by SOC and PT ;
- Osimertinib-related serious TEAEs by SOC and PT;
- G1T38-related and Osimertinib-related serious TEAEs by SOC and PT;
- G1T38-related or Osimertinib-related serious TEAEs by SOC and PT;
- Grade 3 or higher TEAEs by PT;
- Grade 3 or higher G1T38-related TEAEs by PT;

- Grade 3 or higher Osimertinib-related TEAEs by PT;
- G1T38 or Osimertinib-related, Grade 3 or higher TEAEs by PT;
- G1T38 and Osimertinib-related, Grade 3 or higher TEAEs by PT;
- TEAEs leading to G1T38 reduction by SOC and PT
- TEAEs leading to G1T38 discontinuation by SOC and PT;
- TEAEs leading to Osimertinib discontinuation by SOC and PT;
- TEAEs leading to G1T38 and Osimertinib discontinuation by SOC and PT;
- TEAEs leading to death by SOC and PT

Where a patient has the same adverse event, based on preferred terminology, reported multiple times, the patient will only be counted once at the preferred terminology level in adverse event frequency tables. Where a patient has multiple adverse events within the same system organ class, the subject will only be counted once at the system organ class level in adverse event frequency tables. When reporting adverse events by CTCAE grade, summary table will also be provided based on the most severe grade.

The collapsed preferred terms as mentioned in Table 6-1 and Table 6-2 will be presented unless otherwise specified. In summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT according to the overall group. In summaries by PT, AEs will be sorted by decreasing frequency according to the overall group. Summaries will be provided by dose level for the safety population.

Listings will be presented for all AEs with details including dictionary SOC/PT (non-collapsed), verbatim term, start/stop dates (non-imputed) and duration, severity grade, drug-relationship, action taken, and outcome. Listings will be flagged with during treatment period, prior-treatment or post-treatment period.

Listings will be repeated for all serious adverse events (SAEs), AEs leading to discontinuation of any study drug, and AEs with a fatal outcome.

Vital Signs

For vital sign parameters, the observed values and changes from Baseline will be summarized using descriptive statistics for each scheduled visit, last assessment during treatment period, and maximum and minimum post-baseline values during treatment period.

Additionally, the proportions of subjects who meet the potentially clinically significant criteria, defined in Table 7, will be tabulated as at any time during the treatment period.

A listing of observed vital signs values and change from baseline with the abnormality flag by subject will be produced.

ECOG Performance Status

ECOG performance status will be summarized using descriptive statistics at each scheduled visit during the treatment period. Number and percentage of patients will be summarized for each status. In addition, the maximum post-baseline performance status during treatment period will be presented, including assessment at unscheduled visits.

ECOG performance status (0, 1, 2, 3, 4, and 5) will be listed.

Electrocardiograms

ECG parameter (e.g., QT interval corrected by Fridericia's formula [QTcF]) observed values and changes from Baseline will be summarized using descriptive statistics for each scheduled visit, last assessment during treatment period and maximum and minimum post-baseline during treatment period. Both scheduled and unscheduled assessments will be used to identify last and worst post-baseline values during treatment period. For the triple assessments as a specific time point, the average will be summarized for that time point.

Incidence of ECG meeting potentially clinically significant criteria (Table 9) will be summarized with frequencies and percentages.

An accompanying listing of subjects will be produced and it will display all ECG measurements collected on CRF together with derived values (RR, QTcB and QTcF) and findings during the study in subjects with abnormal ECGs, as determined by the investigator.

Laboratory Results

For the purposes of summarization in both the tables and listings, all laboratory values will be converted and presented in SI units.

Clinical laboratory parameters observed values, changes from Baseline, and percent changes from Baseline will be summarized using descriptive statistics for each scheduled visit, last value during treatment period, maximum and minimum post-baseline value during treatment period. Last value during treatment period, maximum and minimum values will be based on both scheduled and unscheduled visits. Graphical presentations of median and change from baseline over time will provide additional focus to be placed on absolute neutrophil count.

Toxicities for clinical labs will be characterized according to CTCAE, Version 4.03. Shifts in toxicity grades from baseline to the worst post-baseline value will be summarized. The worst post-baseline values will consider both scheduled and unscheduled data. Any graded abnormality that occurs following the initiation of study drug and represents at least 1- grade increase from the baseline assessment is defined as treatment emergent. Summary of treatment-emergent worst clinical laboratory abnormalities based on CTCAE Grade will be presented. Worst is referring to the worst scenario during the post-baseline period. Hepatic abnormalities will be summarized using frequency tabulation.

Observed values of clinical labs (hematology, chemistry, and urinalysis) and CTCAE grades will included and values outside the normal range will be flagged in the listings of individual subject data. In addition, a separate listing will be prepared for patients who met Hy's law.

Echocardiogram/MUGA

For quantitative echocardiogram/MUGA results, descriptive statistics will be used to summarize parameters based on the observed value and the change from baseline value at each visit.

Echocardiogram/MUGA results will be listed.

Pregnancy Test

The pregnancy test data will be presented in listings.

6. PLANNED ANALYSIS (PART 1)

No formal interim analysis is planned.

The final analysis will be conducted after all Part 1 patients discontinued treatment and database is locked

7. CHANGE FROM THE PROTOCOL (PART 1)

Following changes specified in the protocol are noted:

- Due to an internal G1 corporate strategy shift, the sponsor decided not to open Part 2 of the study. Both original study design and original planned analysis for Part 2 will not be included in this SAP
- The Protocol includes "Final analysis" and "End of study analysis". The SAP includes final analysis for Part 1due to the strategy shift mentioned above .
- In order to reduce any harm or burden to the patients, data of [redacted], data of overall survival and data of subsequent anti-cancer treatment are no longer required (since 29 January 2020). No cfDNA related analysis or the overall survival analysis detailed in the protocol will be conducted for Part 1 due to limited data in Part 1.
- All tumor assessments are conducted by the investigators or site radiologist. No Blinded Independent Central Review (BICR) assessment will be implemented for PFS as opposed to both BICR and investigator assessment mentioned in protocol.
- In the protocol, Hy's law criteria is described as, "AST or ALT $\geq 3 \times$ upper limit of normal [ULN] and total bilirubin $\geq 2 \times$ ULN." Hy's law criteria is defined in the SAP

as, "ALT and/or AST > 3 × ULN x 3 and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN."

- The protocol refers to Clinical benefit rate (CBR), which 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. The SAP replaces the term CBR with Disease Control Rate (DCR) with the same definition.
- The protocol defines time to first objective response as the time from first dose of study drug to first objective response of CR or PR and states, "patients who do not experience objective response of CR or PR will be censored at the last adequate assessment date." The SAP removes the KM analysis for the time to first objective response and calculates time to first objection response for patients who experience objective response only.
- The protocol defines DOR as the time between first objective response of CR or PR and the first date that progressive disease is objectively documented or death and states, "patients who do not experience objective PD or death will not be included in the analysis." The SAP SAP clarifies that the DOR analysis is based on patients who achieve objective response. In addition, the SAP states, "patients who achieve objective response but do not experience objective PD or death will be censored at the last adequate assessment date."

8. REFERENCES

Eisenhauer EA et al, New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1).