Statistical Analysis Plan	
Drug Substance	AZD9291, osimertinib
Study Code	D5161C00003
Version	4.0
Date	27 September 2023

A multicentre, open-label, single-arm, molecular profiling study of patients with EGFR mutation-positive locally advanced or metastatic NSCLC treated with osimertinib

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

A multicentre, open-label, single-arm, molecular profiling study of patients with EGFR mutation-positive locally advanced or metastatic NSCLC treated with osimertinib

Study Statistician

PPD

Date

A multicentre, open-label, single-arm, molecular profiling study of patients with EGFR mutation-positive locally advanced or metastatic NSCLC treated with osimertinib

Global Product Statistician

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Parexel Study Statistician

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
CI	Confidence interval
CM	Concomitant medication
cMET	Proto-oncogene encoding hepatocyte growth factor receptor
CR	Complete response
CrCl	Creatinine Clearance
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour deoxyribonucleic acid
CYP	Cytochrome P450
DCO	Data cut off
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation-positive
FAS	Full analysis set
FDA	US Food and Drug Administration
FPI	First patient in
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin

Abbreviation or special term	Explanation
HER2	Human epidermal growth factor receptor 2
HL	Hy's Law
IB	Investigator brochure
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IP	Investigational product, also referred to as 'study drug' and 'study treatment' in this protocol
IRB	Institutional Review Board, synonymous to Ethics Committee
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
K-M	Kaplan-Meir
LD	Longest Diameter
LVEF	Left ventricular ejection fraction
M1a	Malignant effusion
M1b	Distant metastasis
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NA	Not Applicable
NCI	National Cancer Institute
NE	Not Evaluable
NED	No evidence of disease
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
PAS	Primary analysis set
PD	Progressive disease
PFS	Progression-free survival
PHL	Potential Hy's Law

Abbreviation or special term	Explanation
PID	Percentage intended dose
PR	Partial response
PT	Preferred term
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	A commercially available integrated system of software products, commonly used for reporting and analysis of Clinical Studies
SD	Stable disease
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TFST	Time to first subsequent therapy or death
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TNM	Tumour, Node, and Metastasis Classification of Malignant Tumours
TTD	Time to treatment discontinuation or death
ULN	Upper limit of normal
USA	United States of America
WBDC	Web based data capture
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	6/6/2019	Initial approved SAP	N/A	N/A
Derivation of primary endpoint(s)	1/26/2022	Section 2.1 added new sensitivity analysis set, also updated in Section 6.	No (V4.0)	To allow use of more paired biopsies in the analyses.
Derivation of secondary endpoint(s)	9/17/2021	Section 3.1.2.2.6 clarified censoring rules.	Yes	Not described in CSP in this detail
Derivation of secondary endpoint(s)	9/17/2021	Section 3.1.2.2.7 Clarified definition of best percentage change in TL tumour size.	Yes	Not described in CSP in this detail
Safety endpoint(s)	5/13/2021	Section 3.3.1 Table 7 amended Visit 10 Upper Limit to 196.	Yes	Not described in CSP in this detail
Safety endpoint(s)	10/21/2021	Section 3.3.2.1 Added text on imputation of missing death dates.	Yes	Not described in CSP in this detail
Safety endpoint(s)	5/13/2021	Section 3.3.5 Added corrected calcium formula	Yes	Not described in CSP in this detail
Safety endpoint(s)	5/13/2021	Throughout, updated physical examination analysis as only look at whether it was performed or not.	Yes	Not described in CSP in this detail
Safety endpoint(s)	5/13/2021	Section 4.2.9.4 Removed descriptive statistics section for ECG data.	Yes	Not described in CSP in this detail
Data presentation	9/17/2021	Section 3.3.7 Updated where clinically significant physical examination findings will be recorded.	Yes	

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	9/17/2021	Section 4.3 Clarified mutations will be detected in the tumour. Removed reference to T790m subgroups, no longer presented.	Yes	T790m subgroup had very few subjects, decided not relevant to analyses.
Other	5/13/2021	Section 4.2.5 Deleted the repeated 'primary tumour' and 'Extent of Disease Upon Entry to Study (metastatic, locally advanced, both)'	Yes	Not described in CSP in this detail
Other	5/13/2021	Added new section 4.2.11 on COVID-19 impact and added to section 4.2.2 for COVID-19 related PDs.	No (V4.0)	COVID-19 not covered in CSP. To be updated in CSP amendment.
Other	9/17/2021	Section 4.2.1 Updated to match table 14.1.1 (added: patients ongoing in the study at DCO, and reasons for study discontinuation).	Yes	Not described in CSP in this detail
Other	02/12/2021	Section 3.4 updated to include information about biomarker data for patients who move to another study post progression.	No (V4.0)	To allow for potentially more paired biopsies to be included in the analyses.
Other	15/02/2022	Section 5 updated to include that an interim will be performed using the PAS-ITT analysis set.	Yes	CSP allows for ad hoc interim analyses to be performed.
Derivation of primary endpoint(s)	10/17/2022	Removed PAS-ITT analysis set and updated PAS description to include biopsies up until the next anticancer therapy.	Yes	Updated to match CSP V5.0.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Other	10/17/2022	Updated references of primary analysis to final analysis and clarification of when final analysis will happen. Added definition of study end.	Yes	Updated to match CSP V5.0.
Other	04/21/2023	Section 1.2 updated definition of study end. Added additional paragraph about study end based off CSP, and details on patient management following the final DCO, as well as following study completion.	Yes	Updated to match CSP V7.0
Figure 1	04/21/2023	Replaced Figure 1 with most up to date version of the figure.	Yes	Updated to match CSP V7.0
Table 1	04/21/2023	Updated to match Table 2 in CSP.	Yes	Updated to match CSP V7.0
Number of patients	04/21/2023	Section 1.3 updated to match Synopsis and Section 8.1 in CSP: …' and when approximately 50 patients have evaluable paired biopsies upon progression'	Yes	Updated to match CSP V7.0
Primary Analysis set	04/21/2023	Section 2.1.2 definition updated to match Section 8.3.1 in CSP	Yes	Updated to match CSP V7.0
Table 8 and Laboratory evaluations	04/21/2023	Included Magnesium and creatine phosphokinase to list of laboratory safety assessments to match section 5.2.1 and Table 3 in CSP.	Yes	Updated to match CSP V7.0
LVEF	04/21/2023	Section 3.3.9 updated to match Section 5.2.4 in CSP.	Yes	Updated to match CSP V7.0

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	04/21/2023	Section 4.2.2 added to describe attrition table of biopsy samples requested by AZ.	No	Added to explore why patients who had an evaluable baseline did not have a paired progression sample for the primary analysis.
Primary endpoint and Proportion of patients with a given marker	05/30/2023	Section 4.2.9.1 Added 'Ambiguous' category to 'Pathogenic' and 'Likely Pathogenic'	No	Included because of discrepancy in number of alterations (amplification) in ESMO/ESMO Asia due to missing "ambiguous" amplification call.
Progression-free survival censoring	08/30/2023	Section 3.2.2.1 - Added more detail regarding 2 missing visits when the assessment interval changes from 8-weekly to 10-weekly.	Yes	Prior SAP didn't consider how interval change affected 2 missing visits.
Safety analysis windows and baseline	09/19/2023	Section 3.3.1 - Extended table past 3.5 years. Clarified safety assessment baseline definition	Yes	Prior SAP didn't consider visit interval change at 3.5 years.
Data presentation	09/19/2023	Section 4.2.2 - Added category to cover those patients that progressed yet didn't have a progression biopsy	Yes	To ensure complete categorisation of subjects with baseline biopsy.
Data presentation	09/19/2023	Section 4.1 - Specified that laboratory parameters will be presented with AZ recommended number of decimal places.	Yes	Match AZ presentation of Lab parameters
Baseline for RECIST	09/19/2023	Section 3.1.1, 3.2.2.7 - Specified that baseline will consider Tumour assessments on day of treatment start.	Yes	Added to ensure higher proportion of baseline values for subjects.

1. STUDY DETAILS

1.1 Study Objectives

Primary:

Primary Objective:	**Outcome Measure:**
To examine the genetic and proteomic profile at the point of disease progression in patients receiving osimertinib as first-line Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy for EGFR mutation-positive (EGFRm+) locally advanced or metastatic non-small cell lung cancer (NSCLC) compared to the profile prior to initiation of treatment	Proportion of patients with a given tumour genetic and proteomic marker (including, but not limited to, EGFR mutations, human epidermal growth factor receptor 2 [HER2], and proto-oncogene encoding hepatocyte growth factor receptor [cMET] expression and/or amplification) at the point of disease progression as defined by the Investigator; the choice of markers is dependent on the profile comparison at the point of disease progression and prior to treatment initiation.

Secondary:

Secondary Objectives:	**Outcome Measures:**
To assess the efficacy of osimertinib as first-line EGFR TKI therapy for patients with EGFRm+ locally advanced or metastatic NSCLC.	Progression-free survival (PFS), according to RECIST 1.1 by Investigator assessment, and other selected clinical efficacy endpoints including: • Objective response rate (ORR) • Duration of response (DoR) • Disease control rate (DCR)
To assess the efficacy of osimertinib in patient subgroups defined by molecular profile, including but not limited to: • EGFR Ex19del, T790M or L858R mutation • EGFR Ex19del, T790M or L858R detectable in plasma-derived circulating tumour deoxyribonucleic acid (ctDNA)	Progression-free survival, according to RECIST 1.1 by Investigator assessment, and other selected clinical efficacy endpoints including: • Objective response rate (ORR) • Tumour shrinkage/depth of response, defined as best change from baseline in target lesion tumour size • Time to treatment discontinuation or death (TTD)

	• Important patient and disease characteristics
To further assess the efficacy of osimertinib post progression	• Time to treatment discontinuation or death (TTD) • Time to first subsequent therapy or death (TFST)

Safety:

Safety Objectives:	**Outcome Measures:**
To summarise the safety and tolerability profile of osimertinib as first-line EGFR TKI therapy for patients with EGFRm+ locally advanced or metastatic NSCLC	• Adverse events graded by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 • Clinical chemistry, haematology and urinalysis • Vital signs, physical examination, body weight • Electrocardiogram (ECG) • World Health Organization (WHO) performance status

1.2 Study Design

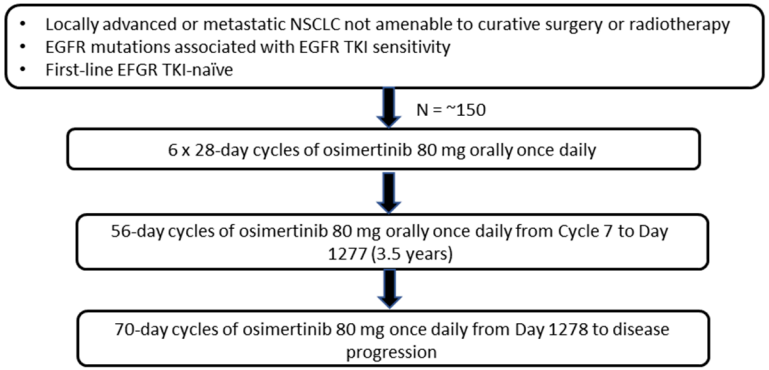
This is a phase II, open-label, single-arm tissue and plasma acquisition study assessing the efficacy and safety of osimertinib (80 mg orally, once daily) as first-line treatment in EGFR TKI treatment-naïve patients with locally advanced or metastatic EGFRm+ NSCLC, and the underlying resistance mechanisms to treatment (Figure 1).

To be eligible, patients must consent to at least 2 mandatory tumour biopsies and have locally advanced or metastatic pathologically confirmed adenocarcinoma of the lung, not amenable to curative surgery or radiotherapy. Patients will have a tumour that harbours one of the EGFR mutations known to be associated with EGFR TKI sensitivity, either alone or in combination with other EGFR mutations (EGFR mutation status determined by a local laboratory). Patients must be EGFR TKI treatment-naïve and eligible to receive first-line treatment with osimertinib.

Patients may continue to show clinical benefit to treatment as judged by the Investigator and continue to receive osimertinib beyond RECIST 1.1-defined progression. Therefore, there is no maximum duration of treatment. On-study assessments are also shown in (Table 1).

A final data cut off (DCO) is planned in Q2 2023, or at the end of the study, when it is estimated that there will be approximately 50 patients with evaluable biopsies at baseline and progression.

Figure 1 Study Flow Chart



	Treatment	Biospecimen Acquisition	Tumour Assessment		Follow -up	
					28-day FU	To first subsequent therapy or death
Pre-treatment		• Tumour tissue [a] • Plasma [a]	At screening		–	–
Before disease progression	As in flow chart above	• Tumour tissue (optional) [a] • Plasma [a, b]	Every 8 weeks up to 3.5 years or disease progression	Every 10 weeks from 3.5 years until disease progression	–	–
At disease progression	May be continued per investigator's judgement	• Tumour tissue [c] • Whole blood [c,d]	–		After last dose of study treatment	–
After disease progression		• Plasma [a, e]	–		–	–

EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.
[a] Analysed at a later date
[b] As per visit schedule until discontinuation of study treatment
[c] Prospective analysis (real time)
[d] A whole blood sample should be taken at the same time (±7 days) as the tumour biopsy at the time of disease progression
[e] If osimertinib is continued beyond investigator-assessed RECIST progression, an additional plasma sample should be taken when osimertinib is stopped

Table 1 Study Schedule – On Study Treatment and Discontinuation

	Screening/ Enrolment [a]	**Treatment Period (further treatment cycles as per C7)** [b]									**Follow-up Period**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days** [c]	**Progression follow-up** [o]
Cycles / Day		**C1**			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
		D1	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±7**	**+7**	**± 7/± 14**
Informed consent	x											
IVRS/IWRS	x											
Demography and baseline characteristics	x											
Medical/surgical history	x											
Inclusion/exclusion criteria	x	x										

	Screening/ Enrolment [a]	**Treatment Period (further treatment cycles as per C7)** [b]									**Follow-up Period**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days** [c]	**Progression follow-up** [o]
Cycles / Day		**C1**			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
		D1	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±7**	**+7**	**± 7/± 14**
Pregnancy test (WoCBP) [p]	x	x										
Tumour tissue sample [d]	x [d]											
Tumour tissue sample on treatment (optional) [e]				x [e]								

	Screening/ Enrolment [a]	**Treatment Period (further treatment cycles as per C7)** [b]								**Follow-up Period**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days** [c]	**Progression follow-up** [o]
Cycles / Day		**C1**			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
		D1	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±7**	**+7**	**± 7/± 14**
Tumour tissue sample upon disease progression [f]										x [f]		
Plasma sample for ctDNA and blood-borne biomarkers	x	x pre-dose	x	x	x	x	x	x	x	x [b, g]		
Whole blood sample at progression [n]										x		

	Screening/ Enrolment [a]	**Treatment Period (further treatment cycles as per C7)** [b]									**Follow-up Period**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days** [c]	**Progression follow-up** [o]
Cycles / Day		**C1**			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
		D1	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±7**	**+7**	**± 7/± 14**
Physical examination, including weight and eyes [h]	x	x			x	x	x	x	x	x		
Height	x											
WHO performance status	x	x			x	x	x	x	x	x		once at start of subsequent anticancer treatment
Vital signs	x	x	x	x	x	x	x	x	x	x		

	Screening/ Enrolment [a]	**Treatment Period (further treatment cycles as per C7)** [b]									**Follow-up Period**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days** [c]	**Progression follow-up** [o]
Cycles / Day		**C1**			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
		D1	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±7**	**+7**	**± 7/± 14**
Clinical chemistry/ Haematology/ Urinalysis [h]	x	x	x	x	x	x	x	x	x	x		
ECG [i]	x	x	x	x	x	x	x	x	x	x		
Echocardiogram/ MUGA (for LVEF) [j]	(x)		At least every 16 weeks up to 3.5 years on study drug and then at least every 20 weeks for as long as on study drug							If clinically indicated		
Tumour assessments (RECIST) [k]	x					x	C5D1 and every 8 weeks until Day 1277		Every 10 weeks until progression			x

	Screening/ Enrolment [a]	**Treatment Period (further treatment cycles as per C7)** [b]									**Follow-up Period**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days** [c]	**Progression follow-up** [o]
Cycles / Day		**C1**			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
		D1	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±7**	**+7**	**± 7/± 14**
Dispense study medication		x			x	x	x	x	x			
Dose with osimertinib				Daily dosing								
Concomitant medication and procedures	x	x	x	x	x	x	x	x	x	x	x	(once) [1]
AEs	x	x	x	x	x	x	x	x	x	x	x	(once) [1]
First subsequent anticancer treatment [m]											x	x

[a] Consent must be taken prior to 28-day screening period. Screening period will start with first study-related assessment.
[b] Six 4-week cycles followed by 8-week cycles from Cycle 7 to 3.5 years (Day 1277), and 10-week cycles from 3.5 years to disease progression. Patients who continue to receive osimertinib beyond RECIST 1.1-defined progression, if continuing to show clinical benefit to treatment as judged by the Investigator, will continue to follow the treatment visit schedule and assessments excluding study specific RECIST assessments and plasma samples for ctDNA and blood-borne biomarkers.
[c] As a minimum, telephone contact should be made with the patient 28 days (window + 7 days) following the discontinuation of study drug (last dose of study drug).
[d] For baseline resistance profiling; testing will be conducted at a later date. The first mandatory tumour tissue biopsy may be an archival or fresh tissue sample obtained within 60 days of study entry. An archival biopsy is acceptable as long as no intervening anticancer treatment occurred since the time the biopsy was obtained to enrolment in this study, and as long as it is within 60 days of study entry.
[e] The optional on-treatment biopsy may be performed between Day 15 and Day 21 of Cycle 1.
[f] The second mandatory tumour tissue biopsy may be performed any time between Investigator-assessed, RECIST 1.1-defined progression and before the start of any new anticancer treatment. If a patient discontinues osimertinib before RECIST 1.1-defined progression, the second biopsy will not be performed.
[g] Plasma samples for ctDNA and blood-borne biomarkers will only be obtained at the treatment discontinuation visit.
[h] If screening assessments have been performed within 14 days prior to starting study treatment, they do not have to be repeated on Visit 2 if the patient's condition has not changed. The assessments are to be completed pre-dose on visit day. Laboratory tests may be performed the day prior to study visits.
[i] ECG is also to be performed in event of any cardiac AE.
[j] To be performed at least every 16 weeks throughout the treatment period up to 3.5 years and then at least every 20 weeks for the remainder of the treatment period. The modality of the cardiac function assessments must be consistent within a patient, ie, if echocardiogram is used for the screening assessment, then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-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.
[k] The screening assessment should be performed within 28 days prior to study drug initiation. Subsequent assessments are to be performed every 8 weeks (± 7 days) from study enrolment until 3.5 years (Day 1277), and then every 10 weeks (± 14 days) until RECIST 1.1-defined progression, even if a patient discontinues treatment prior to progression or receives other anticancer treatment. Tumour assessment will be performed using CT or MRI of the chest, abdomen (including liver and adrenal glands) and pelvis. Any other sites where disease is suspected or known at screening must also be imaged.
[l] If the first scheduled progression follow-up visit falls before the 28-day follow-up visit, then AEs and concomitant medications will be assessed at this visit in addition to the 28-day follow-up visit.
[m] In addition to tumour assessments, patients will be followed for the earlier of first subsequent anticancer treatment (including surgical) after discontinuing osimertinib or death.
[n] At progression, a whole blood sample will be obtained within 7 days of the tissue biopsy being performed.
[o] The progression biopsy should be done prior to the start of subsequent anticancer treatment.
[p] Monthly pregnancy testing and monitoring of WOCBP is recommended, however this schedule may be modified to comply with local legislation.

AE = adverse event; C = cycle; CT = computed tomography; ctDNA = circulating tumour deoxyribonucleic acid; D = day; ECG = electrocardiogram; IVRS/IWRS = interactive voice response system/interactive web response system; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization; WoCBP = women of childbearing potential.

1.3 Number of Patients

It has been determined that approximately 150 patients are appropriate to characterize the frequency of tumour genetic and proteomic markers at disease progression regardless of their prevalence. Table 2 displays the precision of the estimated frequency of mutation when, for example, 50 evaluable paired biopsies are available.

The final analysis will be performed at study end, and when approximately 50 patients have evaluable paired biopsies upon progression. Assuming a 70% of rate of patients having a biopsy at both baseline and progression, and with an assumed technical failure rate of 30% of the samples (assume an overall failure rate of 51%), then we should expect approximately 50 evaluable paired biopsies to be available when approximately 103 of the 150 patients have progressed, which would be expected to occur approximately 38 months after the first patient is enrolled. This calculation assumes patients are recruited over 12 months, exponentially distributed progression times with a 19-month median and a 2-piece recruitment function that assumes an exponentially distributed recruitment rate.

Table 2 Precision of Estimates of Marker Frequency with 50 Available and Evaluable Paired Biopsies

Marker Frequency	95% confidence interval [a]
10%	(3%, 22%)
30%	(18%, 45%)
50%	(36%, 64%)

[a] Exact binomial confidence intervals.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

The primary analysis set (PAS) will be used for the analysis of the primary endpoint. The full analysis set (FAS) will be used for all other efficacy and safety analyses.

2.1.1 Primary analysis set

The PAS will include all patients with evaluable paired biopsies, which are defined as follows: the first biopsy taken prior to osimertinib treatment and the second biopsy taken at any time between Investigator-assessed, RECIST 1.1-defined progression and before the start of any new anticancer treatment. If the Investigator judges the patient to have progressed but the

programmatically defined RECIST progression does not occur, the patient will still be considered evaluable. This analysis set will be used for the analysis of the primary endpoint.

2.1.2 Full analysis set

The (FAS) will include all patients who receive at least one dose of osimertinib. The FAS will be used for all efficacy and safety analyses.

Table 3 summarises the population analysis sets for each outcome variable.

Table 3 Summary of outcome variables and analysis populations

Outcome variable	Population
Primary objective	
Proportion of patients with a given marker at progression as defined by the investigator	PAS
Efficacy data	
PFS, ORR, DoR, DCR, TTD, TFST	FAS
Subgroup analysis	
PFS, ORR, Best change in TL tumour size, TTD	FAS
Important patient and disease characteristics	FAS, PAS
Demography data	
Important patient and disease characteristics	FAS, PAS
Safety data	
Exposure	FAS
AEs	FAS
Laboratory measurements	FAS
Vital signs	FAS
Physical examinations	FAS
Electrocardiograms (ECGs)	FAS

Abbreviations: AEs = Adverse events; DCR = Disease control rate; DoR = Duration of response; ECG = Electrocardiogram; FAS = Full analysis set; ORR = Objective response rate; PAS = Primary analysis set; PFS = Progression free survival; TFST = Time to first subsequent therapy or death; TL = Target lesion; TTD = Time to treatment discontinuation or death.

2.2 Protocol deviations

The following general categories will be considered important protocol deviations which will be listed and discussed in the clinical study report (CSR) as appropriate for the study:

- Informed consent procedure deviation (eg, no informed consent signed prior to any screening procedure)
- Eligibility criteria deviation (eg, any inclusion criteria not met or exclusion criteria met)
- Received prohibited concomitant medications (or unable to stop use prior to receiving the first dose of study drug) or herbal supplements known to be potent inducers of cytochrome P450 (CYP) 3A4 (at least 3 weeks prior). Please refer to protocol Section 3.5 for those medications that are detailed as 'not to be administered' or being 'restricted concomitant medications'. These will be used as a guiding principle for the physician review of all medications prior to database lock.
- Management of adverse events: Lack of prompt reporting of cases meeting Hy's law criteria and serious adverse events (SAE) not being reported within 24 hours of awareness of the event.
- Tumour biopsy sample taken from lesion selected for RECIST assessment (unless only one lesion exists and the RECIST scans are performed within 14 days of screening biopsy).
- No baseline RECIST 1.1 assessment before start of treatment.
- RECIST 1.1 assessments not done every 8 weeks (±7 days) in relationship to the date of first dose until RECIST 1.1 defined progression.
- Screening assessment not performed within 42 days prior to study drug initiation.

If the number of deviations which are considered to have the potential to impact the primary analysis is considered important, sensitivity analyses may be performed on subgroups. This will be decided during the data review meeting and before the database lock. The final classification of protocol deviations will be made prior to database lock. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy

3.1.1 Derivation of RECIST visit responses

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine if, and when, a patient has progressed in accordance with RECIST and their best objective response to study drug.

Baseline radiological tumour assessments are to be performed no more than 28 days before the first dose of treatment, and as close as possible to the start of study treatment. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. Tumour assessments are then performed every 8 weeks (±1 week) following the start of study treatment until objective disease progression.

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

From the Investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE), (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Table 4 for the definitions of CR, PR, SD, and PD.

RECIST outcomes (ie, PFS, ORR etc.) will be calculated programmatically for the site Investigator data (see Section 3.2) from the overall visit responses.

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been irradiated and not chosen for biopsy during the screening period.

3.1.1.1 Target lesions

Measurable disease is defined as having at least one measurable (by RECIST 1.1) lesion, that has not been previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously resected or irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is

recorded, then measurements from the one that is closest and prior to first dose of treatment will be used to define the baseline sum of TLs. Target lesions should be selected based on their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Table 4 provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 4 TL visit responses

Visit Responses	Description
CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of the diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of at least 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
NE	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
NA	No TLs are recorded at baseline.

Abbreviations: CR = Complete response; NA= Not applicable; NE = Not evaluable; PD = Progressive disease; PR = Partial response; SD = Stable disease; TL = Target lesion.

Rounding of TL data

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

Missing TL data

For a visit to be evaluable, all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥5 mm, from nadir (defined below) even assuming the non-recorded TLs have disappeared.

The nadir (ie, the smallest measurement based on the same set of lesions at baseline and on a given visit) can only be taken from assessments where all the TLs had a longest diameter (LD) recorded.

Lymph nodes

For lymph nodes, if the size reduces to <10 mm, these are considered non-pathological.

However, a size will still be measured, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are <10 mm and all other TLs are 0 mm, then although the sum may be >0 mm, the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR response can only be followed by CR, PD or NE. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (ie, 0 mm or <10 mm for lymph nodes), the response will be set to CR irrespective of whether the criteria for PD of TL is also met for lymph node (ie, if a lymph node LD increases by 20% but remains <10 mm).
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0 mm or <10 mm for lymph nodes), the response will be set to NE irrespective of whether the criteria for PD is also met when referencing the sum of TL diameters.
- Step 3: If not all lesions meet the CR criteria, and the sum of lesions meets the criteria for PD, the response will be set to PD.
- Step 4: If, after steps 1 through 3, a response can still not be determined, the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure, this should be indicated in the database and an estimated size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

Irradiated lesions/lesion intervention

Previously irradiated lesions (ie, lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes) which has had intervention during the study (for example, irradiation/palliative surgery/embolization) should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study, noting that an intervention will most likely shrink the size of tumours:

- Step 1: The diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and, if ≤1/3 of the TLs have missing measurements, scale up as described in the scaling section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: If after both steps PD has not been assigned, then, if appropriate (ie, if ≤1/3 of the TLs have missing measurements), the scaled sum of diameters as calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10 mm for lymph nodes) and the lesions that have been subject to intervention also has a value of 0 recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set to NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If >1/3 of TL measurements are missing (because of intervention) then the TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (ie, if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5 mm from nadir).

If ≤1/3 of the TL measurements are missing (because of intervention) then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters) and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion 5 is missing at the follow-up visit; the nadir TL sum including lesions 1-5 was 74mm.

The sum of lesions 1 to 4 at the follow-up visit is 68 mm. The sum of the corresponding lesions at the nadir visit is 62mm.

Scale up as follows to give an estimated TL sum of 81mm:

$$\frac{74}{62} \times 68 = 81\text{mm}$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled-up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split

If a TL splits into two or more parts, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two or more TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size(s) should be recorded as 0 cm.

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method of assessment occurs, between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (eg, CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.1.2 Non-target lesions and new lesions

At each visit, an overall assessment of the NTL response should be recorded by the Investigator. Table 5 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit. Non-target lesion response will be derived based on the investigator's overall assessment of NTLs.

Table 5 NTL visit responses

Visit Responses	Description
CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<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 may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
NA	Only relevant if there are no NTLs at baseline.

Abbreviations: CR = Complete response; NA = Not applicable; NE = Not evaluable; PD = Progressive disease; NTL = Non-target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered as a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

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.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank, this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

Symptomatic progression is not a descriptor for progression of NTLs or TLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs or TLs.

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments, where possible, until objective disease progression is observed.

3.1.1.3 Overall visit response

Table 6 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 6 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR (or NA)	No (or NE)	CR
CR	Non CR/Non PD or NE	No (or NE)	PR

PR	Non PD or NE or NA	No (or NE)	PR
SD	Non PD or NE or NA	No (or NE)	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	Non PD or NE or NA	No (or NE)	NE
NA	CR	No (or NE)	CR
NA	Non CR/Non PD	No (or NE)	SD
NA	NE	No (or NE)	NE
NA	NA	No (or NE)	NED

Abbreviations: CR = Complete response; NA = Not applicable (only relevant if there were no NTLs at baseline); NE = Not evaluable; NED = No evidence of disease; NTL = Non-target lesion; PD = Progressive disease; PR = Partial response; SD = Stable disease.

3.2 Efficacy variables

3.2.1 Primary endpoint

The primary endpoint is the proportion of patients with a given genetic and proteomic marker (including, but not limited to, EGFR mutations, HER2, and cMET expression and/or amplification) at the point of RECIST disease progression as defined by the Investigator; the choice of markers is dependent on the profile comparison at the point of disease progression and prior to treatment initiation. The number of patients with a given genetic and proteomic marker will be divided by the number of patients who have evaluable paired biopsies and have progressed according to the Investigator to calculate the proportion with a given marker at progression. New markers will be defined (for an individual patient) to be those present at progression that were not present at baseline. Only markers defined as 'Pathogenic', 'Likely pathogenic' or 'Ambiguous' by the analysing lab will be tabulated.

3.2.2 Secondary endpoints

From the Investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (unless there is evidence of progression in which case the response will be assigned as progressive disease).

3.2.2.1 Progression-free survival

PFS is defined as the time from the first dose of osimertinib until the date of RECIST 1.1-defined progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. PFS is calculated in months as follows:

$$PFS = \frac{date\ of\ objective\ disease\ progression\ or\ censoring - date\ of\ first\ dose\ of\ osimertinib + 1}{30.4375}$$

Patients who have not progressed or died at the date of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment.

However, if the patient progresses or dies after two or more missed visits (126 days), the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment.

Given the scheduled visit assessment scheme (i.e., eight-weekly for the first 3.5 years [D1277] then ten-weekly thereafter) the definition of 2 missed visits will change. Due to a delay in enacting CSP version 5.0 there was some variability in when patients transitioned to 10-weekly visit. However, we will apply the following rules to all patients.

1. If the previous RECIST 1.1 assessment is baseline, then two missing visits will equate to 17 weeks since the previous RECIST 1.1 assessment, allowing for a late visit (i.e., 2 x 8 weeks + 1 week for a late assessment = 17 weeks [119 days]).
2. If the previous RECIST 1.1 assessment is post baseline and ≤ study day 1169, then two missing visits will equate to 18 weeks since the previous RECIST 1.1 assessment, allowing for early and late visits (i.e., 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks [126 days]).
3. If the previous RECIST 1.1 assessment study day is > 1169 and ≤ 1225, then the two missed visits occur over the period when the scheduled frequency of RECIST 1.1 assessments changes from eight-weekly to ten-weekly, then this will equate to 21 weeks (i.e., take the average of 8 and 10 weeks which gives 9 weeks and then apply same rationale, hence 2 x 9 weeks + 1 week for an early assessment + 2 week for a late assessment = 21 weeks [147 days]).
4. If the previous RECIST 1.1 assessment study day is > 1225 (when the scheduling changes to ten-weekly assessments), two missing visits will equate to 24 weeks (i.e., 2 x 10 weeks + 2 week for an early assessment + 2 week for a late assessment = 24 weeks [168 days]).

If the patient has no evaluable post-baseline visits or does not have baseline data, they will be censored at Day 1 unless they die within two visits of baseline (16 weeks plus 1 week allowing for a late assessment within the visit window).

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the RECIST assessment/scan dates contributing to a particular overall visit assessment.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Objective progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) and an absolute increase of >5 mm, or an overall non-target lesion assessment of progression or a new lesion.

3.2.2.2 Objective response rate

ORR is defined as the percentage of patients with a confirmed investigator-assessed response of CR or PR and will be based on all treated patients with measurable lesions at baseline.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging no less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) and then respond will not be included as responders in the ORR (ie, both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient has 2 non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

3.2.2.3 Duration of response

Duration of response (DoR) will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used

for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed. If a patient does not progress following a response, then their DoR will use the PFS censoring time.

3.2.2.4 Disease control rate

Disease control rate (DCR) is defined as the percentage of patients who have a best overall response of complete response or partial response or stable disease at ≥8 weeks. Patients must have lesions (either TLs or NTLs) recorded at baseline to be included in the denominator. The 8-week time point will allow for a visit window and be defined as on or after study day 49 (allowing for the visit window).

3.2.2.5 Time to treatment discontinuation or death (TTD)

Time to study treatment discontinuation or death (TTD) is defined as the time from first dose of osimertinib to the earlier of the date of study treatment discontinuation or death (ie, date of study treatment discontinuation/death or censoring – first dose of osimertinib + 1). Any patient not known to have discontinued treatment or not known to have died at the time of the analysis will be censored at the last known time to have not discontinued treatment, ie, the last follow-up visit where this was confirmed.

3.2.2.6 Time to first subsequent therapy or death (TFST)

The TFST will be defined as the time from the date of first dose of osimertinib to the earlier of the date of anticancer therapy start date following study treatment discontinuation, or death. Any patient not known to have had a subsequent therapy or not known to have died at the time of the analysis will be censored at the earlier of their last known to be alive date or study termination date.

3.2.2.7 Best percentage change in TL tumour size

The percentage change from baseline in TL tumour size will be calculated every 8 weeks. This is based on RECIST TL measurements taken at baseline. Tumour size is the sum of the longest diameters of the TLs. TLs are measurable tumour lesions. Baseline is defined as in Section 3.1.1. The percentage change in TL tumour size is calculated by

$$\frac{TL\ tumour\ size - baseline\ TL\ tumour\ size}{baseline\ TL\ tumour\ size} \times 100\%.$$

The best percentage change in TL size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction over the course of the study and will include all assessments prior to the earliest of death in the absence of progression, any evidence of

progression, the start of subsequent anticancer therapy. A negative change denotes a reduction in target lesion size.

3.3 Safety variables

Safety and tolerability will be assessed in terms of AEs, SAEs, AEs leading to discontinuation, laboratory data (including clinical chemistry, haematology and urinalysis), vital signs, physical examinations, ECGs and World Health Organization (WHO) performance status.

3.3.1 General considerations for safety assessments

Time windows will need defining for any presentations that summarise values by visit (Table 7). The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus one day.
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit-based summaries, if there is more than one value per patient within a time window then the value closest to the planned study day should be summarised, or the earlier in the event the values are equidistant from the planned study day. The listings should highlight the value for that patient that went into the summary table, wherever feasible.
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.
- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment. Where safety data are summarised over time, study day will be calculated in relation to date of first study treatment. For safety endpoints the last observation before the first dose of IP will be considered the baseline measurement unless otherwise specified. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.
- Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (ie, below the lower limit of quantification) or >x (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

Table 7 Visit number and corresponding study day

CRF visit	Target day	Actual assessment day	Analysed visit
Visit 1	D-28	D-28 - D-1	Screening
Visit 2	D1	D1	Day 1
Visit 3	D8	D2-D11	Week 1
Visit 4	D15	D12-D21	Week 2
Visit 5	D29	D22-D42	Week 4
Visit 6	D57	D43-D70	Week 8
Visit 7	D85	D71-D98	Week 12
Visit 8	D113	D99-D126	Week 16
Visit 9	D141	D127-D154	Week 20
Visit 10	D169	D155-D196	Week 24
Visit 11	D225	D197-D252	Week 32
Visit 12	D281	D253-D308	Week 40
Visit 13	D337	D309-D364	Week 48
Visit 14	D393	D365-D420	Week 56
Visit 15	D449	D421-D476	Week 64
Visit 16	D505	D477-D532	Week 72
Visit 17	D561	D533-D588	Week 80
Visit 18	D617	D589-D644	Week 88
Visit 19	D673	D645-D700	Week 96
Visit 20	D729	D701-D756	Week 104
Visit 21	D785	D757-D812	Week 112
Visit 22	D841	D813-D868	Week 120
Visit 23	D897	D869-D924	Week 128
Visit 24	D953	D925-D980	Week 136
Visit 25	D1009	D981-D1036	Week 144
Visit 26	D1065	D1037-D1092	Week 152
Visit 27	D1121	D1093-D1148	Week 160
Visit 28	D1177	D1149-D1204	Week 168
Visit 29	D1233	D1205-D1267	Week 176
Visit 30	D1303	D1268-D1337	Week 186
Visit 31	D1373	D1338-D1407	Week 196
Visit 32	D1443	D1408-D1477	Week 206
Visit 33	D1513	D1478-D1547	Week 216
Visit 34	D1583	D1548-D1617	Week 226
Visit 35	D1653	D1618-D1687	Week 236
Visit 36	D1723	D1688-D1757	Week 246
Visit 37	D1793	D1758-D1827	Week 256
Visit 38	D1863	D1828-D1897	Week 266

CRF visit	Target day	Actual assessment day	Analysed visit
Visit 39	D1933	D1898-D1967	Week 276
Visit 40	D2003	D1968-D2037	Week 286
Visit 41	D2073	D2038-D2107	Week 296
Visit 42	D2143	D2108-D2177	Week 306
Visit 43	D2213	D2178-D2247	Week 316
Visit 44	D2283	D2248-D2317	Week 326
Visit 45	D2353	D2318-D2387	Week 336

3.3.2 Handling missing data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing with the exceptions specified for certain efficacy variables.

3.3.2.1 Imputation of partial dates

Concomitant medication and adverse events start dates

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st.
- If year and month are present and day is missing, impute day as first day of the month.

Concomitant medication and adverse events end dates

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as December 31st, unless this is after the date of death in which case date of death will be used instead.
- If year and month are present and day is missing, impute day as last day of the month, unless this is after the date of death in which case date of death will be used instead.

In addition, for AEs and CMs if, for a partial start date, the start date could (when also considering the end date) potentially be on the first study medication date, the start date will be imputed with the first study medication date to assume a "worst case" scenario; eg, AE from UNK-Feb-2014 to 23-Mar-2014 with first study medication date 21-Feb-2014, then the AE start date will be imputed to 21-Feb-2014.

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- For Missing day only – using the 1st of the month

- For Missing day and Month – using the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, ie, censored at the last known alive date.

3.3.3 Exposure and dose interruptions

Osimertinib will be taken once daily and exposure will be defined as follows:

Total (or intended) exposure of study treatment (days)

- Total (or intended) exposure = min(last dose date where dose > 0mg, date of death, date of DCO) – first dose date + 1

Actual exposure of study treatment (days)

Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above and a dose interruption is defined as any length of time where the patient has not taken any of the planned daily dose. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Missed and forgotten doses should be recorded on the EX module as a drug interruption with the reason recorded as "Subject forgot to take dose". These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC will be used in the programming.

Safety Follow-up

Total safety follow-up will be calculated as follows:

- Total Safety Follow-up = min([last dose date + 28 days], date of withdrawal of consent, date of death, date of DCO) – first dose date +1

3.3.4 Adverse events

AEs and SAEs will be collected from the date of informed consent, throughout the treatment period and including the 28-day follow-up period after the last dose of treatment. Events will be defined as treatment emergent if they start or worsen (by Investigator report of a change in intensity) during the treatment period as defined in the protocol (date of first dose to 28 days post

last dose, inclusive). The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code the AEs. AEs will be graded according to the latest version of the National Cancer Institute Common Terminology Criteria for AEs (CTCAE).

3.3.5 Laboratory variables

Laboratory data will be collected throughout the study, from screening to treatment discontinuation as per the study plan described in the protocol. These include blood and urine samples for determination of clinical chemistry, haematology and urinalysis. For the definition of baseline and the derivation of post baseline visit values considering visit windows and how to handle multiple records, derivation rules as described in Section 3.3.1 will be used. If screening assessments have been performed within 14 days prior to starting study treatment, they do not have to be repeated on Visit 2 if the patient's condition has not changed. The assessments are to be completed pre-dose on the visit day.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. The laboratory variables defined in Table 8 will be measured.

Table 8 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hb	S/P-Creatinine
B-Leucocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-ALP
B-Platelet count	S/P-AST
	S/P-ALT
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Magnesium

	Creatine phosphokinase

ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = blood; Hb = haemoglobin; P = plasma; S = serum; U = urine.

At each visit, approximately 6 mL of blood for clinical chemistry and 9 mL for haematology will be taken. The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities.

Change from baseline in clinical chemistry, haematology and urinalysis variables will be calculated for each post-dose visit on treatment. Common toxicity criteria (CTC) grades will be defined at each visit according to the CTC grade criteria using local or project ranges as required, after conversion of lab result to corresponding project-wide preferred units.

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). As applicable, values will be converted to standard units and will be graded using CTCAE version referenced in the Clinical Study Protocol. Corrected calcium(x) records will be programmatically derived, using below formula, and appended to the lab dataset for grading.

$$Corrected\ calcium\ (mmol/L) = Total\ calcium\ (mmol/L) + ([40 - albumin\ (G/L)]\ x\ 0.02)$$

The maximum (or minimum) on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value up until treatment discontinuation.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTC grades will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTC criterion involves a change from baseline, evaluable patients would have both a baseline and at least 1 post-dose value recorded.
- If a CTC criterion does not consider changes from baseline, to be evaluable the patient needs only to have 1 post dose-value recorded.

3.3.6 Vital signs

Vital signs data (blood pressure, pulse and temperature) will be obtained at every visit up until treatment discontinuation and will be used for reporting. Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. For derivation of post-baseline

visit values, considering visit window, and to handle multiple records, derivation rules as described in Section 3.3.1 will be used.

3.3.7 Physical Examinations

Physical examination data (indication whether data were collected or not) will be obtained at the start of each cycle (including screening) up until treatment discontinuation. Clinically significant findings at screening will be recorded in surgical or medical history. Any new or aggravated clinically relevant abnormal medical finding at a physical examination will be reported as an AE.

3.3.8 Electrocardiograms

Electrocardiogram (ECG) data (details of rhythm, ECG intervals and an overall evaluation) will be obtained at every visit until treatment discontinuation. If there is an abnormal on-treatment assessment at the time of treatment discontinuation then a 28-day follow-up assessment will be required to confirm reversibility of the abnormality.

3.3.9 Left ventricular ejection fraction (LVEF)

An echocardiogram or multigated acquisition scan (MUGA) to assess LVEF will be performed at screening (prior to first dose of osimertinib) and at least every 16 weeks throughout the treatment period until patients have reached 3.5 years on the study. Thereafter, echocardiogram or MUGA will be performed at least every 20 weeks for the remainder of the treatment period. Additional assessments of LVEF should be performed as clinically indicated. A 28-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.

3.3.10 Ophthalmological assessments

Full ophthalmic assessment, including slit lamp examination, will be performed if a patient experiences any visual symptoms (including blurring of vision). Ophthalmology examination results should be collected in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE.

3.4 Biomarker variables

If a patient progresses in the ELIOS study and then enrols in a subsequent AZ study, and if appropriate consent is provided, the biomarker results from a progression biopsy (generated in

either the other study or ELIOS), may be shared between both studies and the data may be analysed as part of the ELIOS study.

Biological samples, other than those collected for the primary objective, will be collected and may be analysed for CCI [redacted]

4. ANALYSIS METHODS

4.1 General principles

The following general principles will be followed throughout the study:

- Continuous variables will be summarised by the number of observations, mean, standard deviation, median, 1st and 3rd quartiles (where applicable), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place, and the standard deviation will be reported to two more decimal places, than the raw data recorded in the database. For laboratory data the recommended number of decimal places per parameter will be used rather than raw data precision.
- Percentages will be presented to one decimal place.
- SAS® version 9.3 or later will be used for all analyses.

Study Day 1 is defined as the date of first dose of study drug. For visits (or events) that occur on or after first dose, study day is defined as (date of visit [event] - date of first dose of study drug + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] - date of first dose of study drug). There is no Study Day 0.

For safety endpoints the last observation before the first dose of study drug will be considered the baseline measurement unless otherwise specified.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value ×100.

The primary analysis will be based on the PAS. All secondary efficacy, safety, study population and demography data will be summarised and analysed based on the FAS.

The final analysis timepoint, at study end, and when approximately 50 patients have evaluable paired biopsies upon progression, will include production of all the tables, listings and figures, which will be specified and finalised in a separate TLF shell document before database lock.

4.2 Analysis methods

4.2.1 Patient disposition

The total number of patients screened (including screening failures), enrolled (ie, patients with informed consent), patients who received any study drug and patients who did not receive any study drug, patients ongoing treatment at DCO, patients ongoing in the study at DCO, patients who completed treatment, patients who discontinued treatment and the reason for discontinuation, and patients who discontinued the study and the reason for discontinuation will be summarised.

The number and percentage of patients included in the analysis populations and the number of patients recruited by country and centre will be also presented.

4.2.2 Attrition of biopsy samples

To explore why patients who had an evaluable baseline did not have a paired progression sample for the primary analysis, the total number of patients that had a baseline biopsy, the number of patients that had a baseline biopsy that was not evaluable, and the number of patients that had an evaluable baseline biopsy will be summarised. The number of patients that had not progressed at DCO, withdrew from the study prior to progression, died prior to progression, did not have a biopsy after progression, had a progression biopsy that was not evaluable, or had an evaluable progression biopsy will be further summarised for patients that had an evaluable baseline biopsy.

4.2.3 Protocol deviations

All identified important protocol deviations will be listed and summarised for the FAS. All protocol deviations will be defined by the study team and identified and classified as important or not important before database lock. All important protocol deviations confirmed to be due to Coronavirus Disease 2019 (COVID-19) will be summarised.

4.2.4 Demographics and other baseline characteristics

Demographic and baseline subject characteristics will be listed and summarised for the FAS and the PAS and defined subgroups by mutation status. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (kg/m^2), calculated as: $\frac{weight}{height^2}$
- Nicotine consumption (number of pack years)

The total counts and percentages of patients will be presented for the categorical variables of:

- Age group (years) (grouped as <50, ≥50-<65, ≥65-<75, ≥75)
- Sex
- Race
- Ethnic group
- Smoking status.
- WHO performance status (0/1)
- EGFR mutation type (Ex19del, L858R)

4.2.5 Medical history

Relevant medical history (past and current) and relevant surgical history will be coded using the most recent version of MedDRA.

All medical history will be summarised (number and percentage of patients) for the FAS by system organ class (SOC) and preferred term (PT).

4.2.6 Disease history

The following disease characteristics will be summarized for all patients in the FAS (unless specified otherwise), the PAS and defined subgroups by mutation status:

- Disease characteristics at baseline (time from original diagnosis, primary tumour location, histology type, regional lymph nodes, distant metastases, stage/ American Joint Committee on Cancer [AJCC] stage).
- Extent of disease upon entry to study (metastatic/locally advanced, site of metastatic disease).
- Previous cancer therapy (Neo-adjuvant, adjuvant chemotherapy, any previous radiotherapy, any previous surgery).

- EGFR mutation status
- Site of local/metastatic disease
- Brain metastases and Visceral metastases
- Baseline TL size (mean and categories: <40, 40-79, 80-119, ≥120mm)
- Histology type

4.2.7 Concomitant medication

Prior and concomitant medications are defined as follows:

- Prior medications are medications taken prior to or during screening with a stop date prior to the first dose of study drug
- Concomitant medications are medications with or without a stop date on or after the date of first dose of study drug (and could have started prior to or during treatment).

Concomitant medication will be summarised using frequency tables by Anatomical therapeutic chemical (ATC) classification code (based on World Health Organisation (WHO) classification).

4.2.8 Exposure

The following summaries will be produced for the FAS and the PAS:

- Total exposure to study treatment,
- Actual exposure to study treatment
- Number of and reasons for dose interruptions
- Number of and reasons for dose reductions
- Time on study – defined as the time in days from the start date of treatment to the date of last study assessment or the date of withdrawal.

4.2.9 Primary and Efficacy Endpoints

Table 9 presents the formal statistical analyses to be conducted for the primary and efficacy endpoints.

Table 9 Formal analyses

Endpoints analysed	Notes
Proportion of patients with a given genetic and proteomic marker at the point of disease progression as defined by the Investigator	Primary analysis
PFS	Secondary analysis
Objective response rate	

Duration of response

Disease control rate

Subgroup analyses

PFS

Objective response rate

Best change in TL tumour size

Time to treatment discontinuation or death

Time to treatment discontinuation or death

Time to first subsequent therapy or death

4.2.9.1 Proportion of patients with a given marker

The proportion of patients with a given genetic and proteomic marker at the point of disease progression (as defined by the investigator) will be calculated and presented alongside the associated exact binomial 95% Clopper-Pearson (exact) confidence intervals (CIs).

If a reasonable proportion (at least 20%) of patients have a given marker at baseline, the difference in the proportion of patients with that marker between progression and baseline, together with its 95% adjusted Wald CI, may also be calculated.

The primary analysis table will include the frequency and proportion of new pathogenic, likely pathogenic or ambiguous mutations and will be split by gene name and variant-type. Other tables will follow the same layout but will look at pathogenic, likely pathogenic or ambiguous mutations at baseline and all pathogenic mutations at disease progression. New markers will be defined (for an individual patient) to be those present at progression that were not present at baseline. Only markers defined as ‘Pathogenic’, ‘Likely pathogenic’ or ‘Ambiguous’ by the analysing lab will be tabulated.

4.2.9.2 Progression-free survival

PFS will be analysed using Kaplan-Meier (K-M) methodology from which the median and its 95% CI will be provided, together with event rates at clinically important landmarks (ie, at 6, 12, 18 and 24 months).

The treatment status at progression of patients at the time of analysis will be summarised. This will include the number (%) of patients who were on treatment at the time of progression, the number (%) of patients who discontinued study drug prior to progression, the number (%) of patients who have not progressed and were on treatment or discontinued treatment. This will also provide the distribution of the number of days prior to progression for the patients who have discontinued treatment.

Additional supportive summaries

Summary statistics will be given for the number of days from censoring to DCO for all censored patients, see Section 3.2.2.1.

Additional summaries will be produced for the following points:

- The duration of follow-up will be summarised using median time from the treatment start date to the censoring date (date last known to have not progressed) in censored (not progressed) patients only.
- The number and percentage of patients who are censored due to two or more consecutive missed RECIST assessments.
- New lesions (ie, sites of new lesions).

4.2.9.3 Confirmed objective response rate

Objective response rate will be summarised as the proportion of patients with a response (ie, CR/PR indicating a response of CR/PR being recorded at 1 visit and confirmed by repeat imaging no less than 4 weeks later with no evidence of progression between the initial and CR/PR confirmation visit), along with the associated exact binomial 95% CI using the Clopper-Pearson method. Patients in the FAS must have evidence of disease at baseline to be included in the denominator.

4.2.9.4 Duration of response

Duration of response will be analysed using K-M methodology from which the median and 95% CI will be produced with event rates at clinically important landmarks as explained in Section 4.2.9.2. Only patients who have responded (a confirmed response) will be included in the analysis.

4.2.9.5 Disease control rate

Disease control rate will be summarised as the proportion of patients with disease control (ie, an overall response of PR/CR or SD at ≥ 8 weeks), along with the associated exact binomial 95% CI using the Clopper-Pearson method. Patients in the FAS must have evidence of disease at baseline to be included in the denominator.

4.2.9.6 Time to treatment discontinuation or death (TTD)

TTD will be analysed using K-M methodology from which the median and 95% CI will be produced with event rates at clinically important landmarks as explained in Section 4.2.9.2.

4.2.9.7 Time to first subsequent therapy or death (TFST)

TFST will be analysed using K-M methodology from which the median and 95% CI will be produced with event rates at clinically important landmarks as explained in Section 4.2.9.2.

4.2.10 Safety

The following sections describe the planned safety summaries for AEs, SAEs, deaths, laboratory parameters, vital signs, physical examinations and ECGs.

4.2.10.1 Adverse events

Only TEAEs, ie, AEs developing or worsening in severity (from baseline severity) on or after the first day of osimertinib administration up to and including 28 days after the last dose of osimertinib (defined as the treatment period) will be summarised.

Any AE occurring before the first dose of osimertinib and AEs occurring 28 days after last dose will be listed only and not included in the summaries.

Any AEs that occur after a patient has received further therapy for cancer (following discontinuation of osimertinib) will be flagged in the data listings. Any AEs that occur after a patient has received further therapy for cancer within 28 days after discontinuing osimertinib are included in the summaries.

The number of patients experiencing each AE will be summarised by the MedDRA system organ class, MedDRA preferred term and worst CTCAE grade. The number and percentage of patients with AEs in different categories (ie, causally related, maximum reported intensity, CTCAE grade ≥3) will be summarised, and events in each category will be further summarised by MedDRA system organ class and preferred term. Events will be displayed by international SOC order and alphabetical PT. Subjects who report the same AE several times will only appear once in that row.

SAEs and deaths will be summarised.

4.2.10.2 Laboratory evaluations

Laboratory data obtained up until treatment discontinuation will be included in the summary tables. Absolute values and change from baseline for all continuous haematology, clinical chemistry and urinalysis laboratory parameters will be summarised for each visit.

Shift tables for change in grade from baseline by treatment group will be produced. The laboratory parameters for which CTC grade shift outputs will be produced are:

- Haematology: basophils, eosinophils, haemoglobin, B-leukocyte differential count (absolute count), lymphocytes, monocytes, neutrophils and platelets.
- Clinical chemistry: alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bilirubin (total), calcium, creatinine, potassium, and sodium.
- Urinalysis:erythrocytes, glucose and protein.

Hy's law

The following summaries will include the number (%) of patients who have:

- Elevated ALT, AST, and total bilirubin during the study
    - AST or ALT ≥3x ULN and total bilirubin ≥2 × ULN during the study (potential Hy's law): the onset date of ALT or AST elevation should be prior to or on the same date of total bilirubin elevation.

Liver biochemistry test results over time for patients with elevated ALT or AST (ie, ≥ 3 × ULN) and elevated total bilirubin (ie, ≥ 2 × ULN) at any time will be plotted.

Individual patient data where ALT or AST plus total bilirubin are elevated at any time will be listed (ie, ALT and/or AST ≥3 × ULN and total bilirubin ≥2 × ULN, at any time).

4.2.10.3 Vital signs

Vital sign data obtained up until the 28-day safety follow-up visit will be included in the summary tables and will be summarised using descriptive statistics (mean, median, standard deviation, minimum, maximum and number of patients). As detailed in Section 3.3.6, changes from baseline will also be summarised.

4.2.10.4 Electrocardiograms

ECG data obtained up until the 28-day safety follow-up visit will be included in the summary tables. The following parameters will be summarised by visit:

- QTc Interval Fredericia >470 ms (Yes, No)
- Overall Evaluation (Normal, Abnormal)
- Clinical significance (Yes, No)

4.2.11 Exploratory analysis

CCI

[redacted]

4.2.12 Impact on analyses due to COVID-19 pandemic

A summary table of participants with confirmed/ suspected COVID-19 infections will be produced; along with the summary of COVID-related IPDs, as described in Section 4.2.3. Patients affected by COVID-19 will be listed; along with medical history, demographics and AEs for those who have confirmed or suspected COVID-19.

4.3 Subgroup analysis

The efficacy of osimertinib will also be assessed via a subgroup analysis. The subgroup will be performed only for the subgroups with 20 progression events or more. The following groups will be assessed:

- Positive pre-treatment mutations detected in the tumour:
  - EGFR Ex19del
  - L858R mutation

PFS, ORR and TTD will be summarised/ analysed for the subgroups outlined above in the same manner as described in Sections 4.2.9.2, 4.2.9.3 and 4.2.9.6, respectively.

4.3.1 Best change in TL tumour size

The best change in TL tumour size from baseline, (where best change in TL size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction) up until RECIST 1.1 progression will also be summarised for each subgroup.

4.4 Summary of mutations by baseline characteristics

Associations between Baseline markers EGFR mutation (Ex19del, L858R), and patient characteristics (listed below), will be explored through cross-tabulations and descriptive statistics.

- Gender (Male / Female)
- Race (Asian / Non-Asian)
- Age at screening (<65 / ≥ 65)
- Smoking history (Smoker / Non-Smoker)
- Baseline WHO Performance Status (0 / 1)

5. INTERIM ANALYSIS

This is an exploratory study which may inform other studies in the osimertinib development programme and therefore earlier interim analyses may be performed, such interim analyses may not be reported in a formal CSR.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Version 7.0 of the protocol was used when writing the statistical analysis plan.

7. REFERENCES

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