Oncology Statistical Analysis Plan

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A Phase III, Randomised, Controlled, Multi-centre, 3-Arm Study of Neoadjuvant Osimertinib as Monotherapy or in Combination with Chemotherapy versus Standard of Care Chemotherapy Alone for the Treatment of Patients with Epidermal Growth Factor Receptor Mutation Positive, Resectable Non-small Cell Lung Cancer (NeoADAURA)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE(s)	Adverse event (s)
AESI(s)	Adverse event (s) of special interest
AJCC	American joint committee on cancer
ALP	Alkaline phosphatise
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC5	AUC of 5 mg/mL/min
BDRM	Blinded data review meeting
BICR	Blinded independent central review
BP	Blood pressure
CDL	Clinical database lock
CI	Confidence interval
cMET	Mesenchymal-epithelial transition factor
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumour deoxyribonucleic acid
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse events
DBL	Database lock
DCO	Data cut-off
DFS	Disease free survival
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
d.p.	Decimal place
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EGFR	Epidermal growth factor receptor
EGFRm+	epidermal growth factor receptor mutation-positive
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire –Core 30 items
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire – Lung Cancer module
EQ-5D-5L	EuroQoL five dimensions, five level
Ex19del	Exon 19 deletions
FAS	Full Analysis Set
^{18}FDG-PET	18F-fluorodeoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second
FN	False negative
FNA	Fine needle aspiration
FP	False positive
GGT	Gamma-Glutamyl Transpeptidase
GHS	Global health status
Hb	Haemoglobin
HER	Human Epidermal Growth Factor Receptor
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health related quality of life
IASLC	International Association for the Study of Lung Cancer
ICF	Informed consent form
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IgM/G	Immunoglobulin M/G

Abbreviation or special term	Explanation
ILD	Interstitial Lung Disease
IP	Investigational product
IMP	Investigational medicinal product
IV	Intravenous
ITT	Intention-to-treat
K-M	Kaplan-Meier
L858R	Sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position858 in exon21
LDH	Lactate dehydrogenase
LRCI	Likelihood ratio confidence interval
LLoQ	Lower level of quantification
lsmean	Least squares mean
LVEF	left ventricular ejection fraction
MDT	Multi-disciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MPR	Major pathological response
MRD	Minimal residual disease
MUGA	Multi Gated Acquisition Scan
NA	Not applicable
NC	Non-calculable
NCI	National Cancer Institute
NPA	Negative percent agreement
NPV	Negative predictive value
NSCLC	Non-small cell lung cancer
OAE	Other significant adverse events
OPA	Overall percent agreement
OS	Overall survival
PAP	Payer Analysis Plan
PAS	Pharmacokinetic Analysis Set
pCR	Pathological complete response
PD	Progressive disease

Abbreviation or special term	Explanation
PERCIST	PET Response Criteria in Solid Tumours
PET	Positron emission tomography
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
pp	Percentage points
PPA	Positive percent agreement
PPV	Positive predictive value
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PT	Preferred term
Q3W	Every 3 weeks
QD	Once daily
QLQ-C30	Quality of Life Questionnaire –Core 30 items
QLQ-LC13	Quality of Life Questionnaire – Lung Cancer module
QoL	Quality of life
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	Corrected QT interval
QTcF	Frederica's corrected QT interval
RAS	Resected Analysis Set
RBC	Red Blood Cell
REML	Restricted maximum likelihood
RVT	Residual viable tumor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAF	Safety analysis set
SAS®	A commercially available integrated system of software products, commonly used for reporting and analysis of Clinical Studies
SE	Standard error
SMQ	Standardised MedDRA query
SoA	Schedule of assessments

Abbreviation or special term	Explanation
SoC	Standard of care
SOC	System organ class
TBIL	Total bilirubin
TEAE	Treatment emergent adverse events
TN	True negative
TNM	Tumour-Node-Metastasis
TP	True positive
UK	United Kingdom
ULN	Upper limit of normal
ULoQ	Upper level of quantification
WHO	World Health Organization

1. STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses summarised in the NeoADAURA clinical study protocol (CSP). This SAP is based on version 5.0 of the CSP (08 December 2023).

1.1 Study Objectives

Table 1 Study objectives

Primary Objective:	**Endpoint/Variable:**
To determine the efficacy of osimertinib as monotherapy or in combination with chemotherapy compared to chemotherapy alone, as Neoadjuvant treatment	• MPR (defined as ≤10% residual cancer cells in the surgical specimen post-surgery, as assessed per central pathology laboratory)
Secondary Objectives:	**Endpoints/Variables:**
To further assess the efficacy of osimertinib as monotherapy or in combination with chemotherapy compared to chemotherapy alone as Neoadjuvant treatment, by assessment of pathological complete response (pCR), EFS, DFS, downstaging and Overall survival (OS).	• pCR (defined as absence of any residual cancer cell in the surgical specimen assessed post-surgery, as assessed per central pathology laboratory) • N2 to N0/N1 and N1 to N0 downstaging at the time of surgery • EFS • DFS • OS
To assess impact of treatment on patients' disease-related symptoms and health-related quality of life in patients	• Difference between treatment arms in adjusted mean change from baseline in EORTC QLQ-C30 and EORTC QLQ-LC13
To further assess the efficacy of osimertinib as monotherapy or in combination with chemotherapy as compared to chemotherapy alone as Neoadjuvant treatment, in patients with or without EGFRm detectable at screening in plasma-derived circulating-free tumour DNA (ctDNA)	• MPR (defined as ≤10% residual cancer cells in the surgical specimen post-surgery, as assessed per central pathology laboratory)
To compare the baseline tumour EGFR mutation status in screened patients with evaluable results from baseline plasma samples.	• Concordance of EGFR mutation status between tumour deoxyribonucleic acid (DNA) and plasma-derived ctDNA at baseline.
To compare the local cobas® EGFR Mutation Test v2 and FoundationOne® CDx results used for patient selection with the retrospective central cobas® EGFR Mutation Test v2 results from baseline tumour samples.	• Concordance of EGFR mutation status between the local EGFR mutation test results and central cobas® EGFR Mutation Test v2 results from tumour samples.
To characterise the pharmacokinetics (PK) of osimertinib and its metabolites	• PK plasma concentrations of osimertinib, and metabolite AZ5104; and ratio of metabolite to osimertinib for each PK sample

Safety Objectives:	**Endpoint/Variable:**
To assess the safety and tolerability profile of Neoadjuvant osimertinib as monotherapy or in combination with chemotherapy administered prior to surgery compared with chemotherapy alone.	• Adverse events (AEs), graded by Common terminology criteria for adverse events (CTCAE) Version 5.0 • Clinical chemistry, haematology, urinalysis • Vital signs, physical examination, body weight • Electrocardiogram • Left ventricular ejection fraction • ECOG Performance Status • Discontinuations due to AEs • Delay/Time to surgery due to investigational product-related AEs
Exploratory Objectives:	**Endpoints/Variables:**
To compare health resource use associated with Neoadjuvant osimertinib as monotherapy or in combination with chemotherapy versus chemotherapy alone.	• The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data.
To compare tumour metabolism at baseline and following Neoadjuvant osimertinib as monotherapy or in combination with chemotherapy versus chemotherapy alone.	• The proportion of patients who have a complete metabolic response, partial metabolic response, stable metabolic disease, or progressive metabolic disease per PERCIST, as measured with ^{18}FDG-PET uptake and assessed by blinded independent central review • Correlation of metabolic response by PERCIST and pathological response
To perform clinical efficacy analysis by tumour tissue versus FNA used for EGFR mutation confirmation at randomisation (if sufficient data obtained)	• Subgroup analysis of MPR, pCR and EFS for patients randomised by FNA versus tumor tissue biopsy
To collect and store tumour, serum, and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to osimertinib and/or chemotherapy (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between tissue and/or bloodborne biomarkers and selected efficacy endpoints. All samples may be used to support diagnostic development.	• Key genetic, gene expression and proteomic markers to include, but not limited to, EGFR mutations, HER, and proto-oncogene encoding cMET expression and/or amplification
To explore the relationship of blood based minimal residual disease (MRD) with clinical response in during Neoadjuvant and Adjuvant therapies.	• Relationship between molecular evidence of disease and clinical response endpoints (MPR, pCR, EFS, DFS)

To investigate changes in cancer-related genes in both plasma and tumour tissue.	• Relationship between molecular aberrations and response, based on biomarker profile of diagnostic tumour tissue and biopsies taken at disease progression (where available). Similar analyses may also be undertaken using plasma samples.
To collect and store germline DNA for exploration of the role of HLA alleles in developmental toxicity.	• HLA alleles associated with susceptibility to drug related AEs (such as but not limited to hypersensitivity).
To explore ILD characteristics during continued/re-initiated study intervention dosing for participants diagnosed with CTCAE Grade 1 or 2 ILD who continue/re-initiate study intervention.	• Characterisation of ILD with continued/re-initiated dosing after prior Grade 1 or 2 ILD (eg, frequency, severity, duration, time to onset of recurrent or higher grade ILD).

1.2 Study Design

This is a Phase III, randomised, controlled, 3-arm, multi-centre study of neoadjuvant osimertinib as monotherapy or in combination with chemotherapy, versus SoC chemotherapy alone, for the treatment of patients with resectable EGFRm NSCLC. For an overview of the study design, see Figure 1.

Approximately 351 patients with histologically or cytologically documented EGFRm (Ex19del and/or L858R) NSCLC with resectable (clinical stage II to IIIB) disease will be randomised in a 1:1:1 ratio to receive investigators choice of platinum-based chemotherapy plus placebo or osimertinib, or osimertinib alone. Patients will be stratified by disease stage (II versus III), race (non-Asian, other Asian [excluding Chinese living in China], and Chinese living in China), and mutation type (Ex19del versus L858R).

The randomised treatment regimens are as follows:

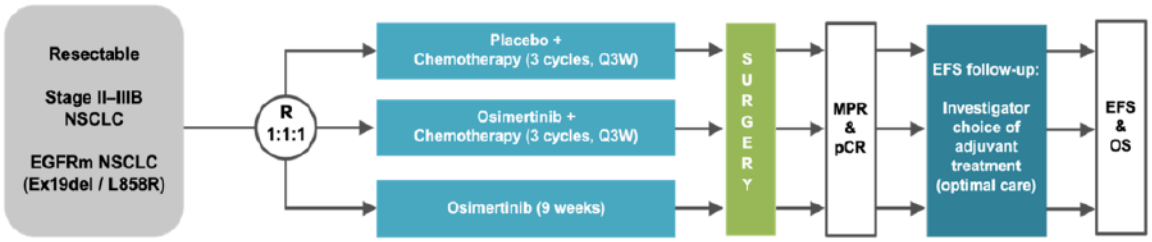
- **Arm 1:** Placebo once daily (QD)+ investigator's choice of chemotherapy (carboplatin AUC5 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2)
- **Arm 2:** Osimertinib 80 mg QD + investigator's choice of chemotherapy (as above)
- **Arm 3:** Osimertinib 80 mg QD as monotherapy

Arms 1 and Arm 2 will be double-blind. Arm 3 will be open label (sponsor-blind).

Prior to randomisation, the Investigator will decide which chemotherapy regimen (carboplatin/pemetrexed or cisplatin/pemetrexed) a patient will receive in the event of randomisation to a chemotherapy containing treatment arm (see above for details of study treatment arms).

The overall study design is shown in Figure 1 below.

Figure 1 Study design



Abbreviations: Ex19del, Exon 19 deletion; NSCLC, Non-small cell lung cancer; EGFRm, mutation-positive epidermal growth factor receptor; R, Randomisation, Q3W, Every 3 weeks; MPR, Major pathological response; pCR, Complete pathological response; EFS, Event-free survival; OS, Overall survival. Patients may receive adjuvant therapy at the discretion of the Investigator (following discussion with MDT), including osimertinib, which will be offered to all patients who have completed surgery (+/- chemotherapy post-surgery and +/- post-operative radiotherapy).

The study primary endpoint is MPR. Secondary endpoints are pathological complete response (pCR), downstaging, EFS, DFS, OS, patient reported outcomes (PROs), and PK.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data at regular intervals throughout the study, including one planned interim analysis for MPR.

Neoadjuvant period

During the neoadjuvant treatment period, patients will be evaluated on Cycle 1 Day 1, and on the first day (-2 to +3 days) of every treatment cycle thereafter (ie, C2D1 and C3D1). For details of the assessments to be performed at each study visit, see study CSP SoA Table 1 (neoadjuvant period).

Each neoadjuvant treatment cycle is 21 days (3 weeks) in duration, unless dosing needs to be held for toxicity reasons. Patients assigned to a chemotherapy-containing arm (Arm 1 or Arm 2) will receive 3 cycles of chemotherapy, in combination with daily treatment with either osimertinib or matching placebo, followed by surgery. Patients assigned to the osimertinib monotherapy arm (Arm 3) will receive daily osimertinib treatment for a minimum of 9 weeks, followed by surgery. Following completion of 3 cycles of chemotherapy in Arms 1 and 2, or 9 weeks of osimertinib monotherapy treatment in Arm 3, patients will then move to the Surgery period.

A study treatment discontinuation visit should be performed only for patients who prematurely discontinued all study treatments in the neoadjuvant period, (ie, prior to completion of 3 cycles), or if a patient fails to undergo surgery following completion of neoadjuvant treatment. For patients who completed 3 cycles of neoadjuvant study treatment and plan to undergo surgery, the pre-surgical assessment visit will take the place of the treatment discontinuation visit. A safety follow-up visit will also be performed 28 days after the last dose of neoadjuvant study treatment or surgery, whichever comes later.

For patients who are deemed ineligible for surgery due to disease progression, the assessment schedule in study CSP SoA Table 2 (Survival period) should be followed thereafter. Patients who did not undergo or complete surgery due to reasons other than disease progression will enter the EFS follow-up period following the neoadjuvant treatment period.

Surgery period

The Surgery period commences at the end of the randomised neoadjuvant period (ie, Day 64 onwards) and ends on the day patient undergoes surgery.

During the Surgery period, the patient should undergo a surgical assessment visit prior to surgery (on D64, -1 to +21 days). Once the pre-surgical assessment visit has been performed, complete surgical resection of the primary NSCLC tumour should be performed as a soon as possible between D64 (start of week 10) and D84 (end of week 12), counted from C1D1 independent of dosing delays or interruptions. In exceptional circumstances (and with prior agreement from the Sponsor study physician) this Surgery period may be extended by 1 additional week (ie, must occur on or before D91, as counted from C1D1 independent of dosing delays or interruptions).

Tumour specimens collected during surgery will be sent to a centralised pathology laboratory to assess pathological response, ideally within 8 weeks after surgery (see study CSP Section 8.1.1 for details).

A Safety Follow-up visit should be conducted 28 days after last dose of the randomised study treatment or 14 days after surgery for patients who underwent resection (whichever is later), which may be completed via the telephone (see CSP SoA Table 1).

EFS follow-up period

All patients who undergo surgery will subsequently enter the EFS follow-up period (see CSP SoA Table 2). Patients that do not undergo or complete surgery for reasons other than disease progression will also enter the EFS follow-up period.

Adjuvant osimertinib will be made available to patients provided by AstraZeneca. If (at the Investigator's discretion) patients are to receive AstraZeneca-supplied adjuvant osimertinib in the EFS follow-up period, this will be regarded as an IP, and patients are required to meet all adjuvant eligibility criteria specified in CSP Section 6.1.2.2 prior to starting AstraZeneca-supplied adjuvant osimertinib. Note that post-operative radiotherapy and chemotherapy are permitted prior to starting AstraZeneca-supplied adjuvant osimertinib treatment.

During the EFS follow-up period, patients who underwent surgery are to be evaluated at the first EFS follow-up visit, 12 weeks post-surgery, at 24 weeks post-surgery, and subsequently every 24 weeks (±14 days) until Week 264 (5-years) post surgery then every 48 weeks (± 14 days) thereafter; or until disease recurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first).

For patients entering the EFS follow-up period who did not undergo or complete surgery due to reasons other than progression, the 12-week visit (and every subsequent EFS follow-up visit) will be calculated from the last day of neoadjuvant treatment.

For details of the assessments to be performed at each study visit, see study CSP SoA Table 2 (EFS follow-up period and survival period). The first contrast enhanced CT scan in the EFS follow-up period should be performed at Week 24 post-surgery, and then at every subsequent visit in the EFS follow-up period, and should use the original neoadjuvant screening scan as a baseline for assessment.

Following surgery, further HRQoL/PRO assessments should also be completed at the first EFS follow-up treatment visit, Week 12 and Week 24 post-surgery visits, and Q24 weeks until Week 264 post-surgery then every 48 weeks (± 14 days), or until disease recurrence, withdrawal of consent, death or until approximately 5.5 years after the last patient is randomised (whichever occurs first).

Survival period

Following disease recurrence or EFS event (if an EFS event takes place before or at the time of surgery), patients will be followed for overall survival every 3 months until death or 5 years from surgery (or from date of last neoadjuvant treatment if no surgery is performed) in the last randomised patient, or until patient withdrawal of consent (whichever occurs first); see study CSP Table 2 (Survival period).

1.3 Number of Patients

Approximately 351 patients will be randomised in a 1:1:1 ratio to three study arms.

The study is sized to characterise the MPR benefit of osimertinib with or without chemotherapy against SoC chemotherapy alone in patients with resectable Stage IIA to Stage IIIB NSCLC. Sample size estimates have been calculated using EAST® version 6.4. For the multiple testing procedure and for details of the alpha allocation, refer to Section 4.2.1.

One interim analysis is planned for the primary endpoint of MPR when approximately half of the patients have had the opportunity to complete surgery and an MPR assessment per central pathology labratory. The final analysis for the MPR endpoint will occur when the last patient has had the opportunity to complete surgery and an MPR assessment (approximately 6 months after the last patient is randomised). The study has approximately 90% power to detect a statistically significant difference in MPR of 20%, with a 2-sided overall significance level of 5% when assuming a 20% MPR in the control arm. The smallest treatment effect that would be statistically significant is a difference in MPR of 11.7% (31.7% in treatment arm versus 20% in control arm).

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomised patients with treatment arms assigned in accordance with randomised treatment allocation, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment are included in the FAS. The analysis of data using the FAS therefore follows the principles of ITT.

The FAS will be used for primary endpoint and all other efficacy analyses except DFS.

Resected Analysis Set (RAS)

The Resected analysis set (RAS) includes all randomised patients who underwent and completed definitive surgical resection (R0). The resected analysis set will be used for DFS endpoint.

Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all randomised patients (i.e. in the FAS) who receive at least 1 dose of study treatment (receive any of osimertinib, placebo, cisplatin, carboplatin, or pemetrexed). Safety data will not be formally analysed but summarised, according to the treatment received; eg, a patient who is randomised to osimertinib plus chemotherapy but who only received osimertinib will be summarised under the osimertinib monotherapy arm.

Pharmacokinetic Analysis Set (PKAS)

Pharmacokinetic Analysis Set (PKAS) is defined as patients in the SAF who have at least 1 measurable PK concentration without any protocol deviation that affects the PK and no missing doses 7 days prior to the PK sample, supported by the relevant date and time of this sample; and, for each time a PK sample was taken (Refer to the CSP Table 1), the dosing data for that day, and for samples taken after multiple dosing, the dosing data for the day prior to the sample day is required.

2.2 Protocol Deviations

Protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

A list of important protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in Table 2, and a list of deviations that are regarded as important are defined in Table 3.

Note that the contents of these tables are not an exhaustive list. A complete list of anticipated protocol deviations (including important protocol deviations) will be compiled separately and finalised prior to database lock.

The number and percentage of patients with an important protocol deviation (listed in Table 3) by type of deviation will be summarised by randomised treatment arm.

In addition to the important protocol deviations, other study deviations captured from the CRF module for inclusion/exclusion criteria will be listed. COVID-19 PDs which are not IPDs will also be listed. Any other deviations observed from medical data review (Physician reports/local lab medical review), monitoring notes or reports may also be reported in an appendix to the CSR. Such deviations which are confirmed to be non-compliant by review will be added to Veeva Clinical Vault (VCV) and this will be used to generate protocol deviation data for analysis.

By-patient listings of protocol deviations will be provided.

Deviation bias will be assessed by repeating the analysis for the primary efficacy endpoint by excluding patients with IPDs that may affect the efficacy of study treatment if greater than 10% of patients have such IPDs. The need for such a sensitivity analysis will be determined

following review of the protocol deviations ahead of the clinical database lock (CDL) to report the study.

Table 2 Protocol deviations with action to be taken for analysis

Protocol Deviation	Act to be taken for analysis
Patient did not receive any study medication	Exclude from safety analysis set
Patient was given incorrect study medication	Analyse "As-randomised" for the FAS. Analyse "As-treated" for the Safety analysis set.

Table 3 Important protocol deviations

Criteria type	Important Deviations Description
IP administration / study treatment	Patient restarted neoadjuvant study treatment after experiencing an ILD event or restarted adjuvant study treatment after Grade >=3 ILD event or Grade 2 ILD without symptom resolution within 4 weeks after dose interruption. Patient did not receive any study medication but was randomised. Patient received/used incorrect investigational product (received different study treatment to that which he/she was randomised).
Inclusion	Complete surgical resection of the primary NCSLC must be deemed achievable.
	Histologically or cytologically documented non-squamous NSCLC with completely resectable (Stage II -IIIB N2) disease (according to Version 8 of the IASLC Cancer Staging Manual [IASLC Staging Manual in Thoracic Oncology 2016]).
	A tumour which harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations (ie, T790M, G719X, Exon20 insertions, S7681 and L861Q).
Exclusion	Prior treatment with any systemic anti-cancer therapy for NSCLC including chemotherapy, biologic therapy, immunotherapy, EGFR-TKI therapy or any investigational drug
	Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD

Criteria type	Important Deviations Description
	Any of the following cardiac criteria: • Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTcF value or by manual calculation; • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, second-degree heart block, and third-degree heart block; • Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as clinically significant electrolyte abnormalities.
Disallowed medications	Other anti-cancer agents, investigational agents or radiotherapy, which are prohibited while the patient is on study treatment. (Adjuvant radiotherapy completed prior to the start of adjuvant IP osimertinib is permitted.)
Procedures/ Tests	The scans for EFS and DFS were not performed in accordance with the protocol visit schedule within one month. Failure to submit surgery sample to central lab (if patient had surgery that was completed).

3. PRIMARY AND SECONDARY VARIABLES

3.1 Surgical specimen assessment

Surgical specimens, including primary tumours, lymph nodes and margins (and pleural lavage cytology if applicable) should be locally assessed first before sending for pathological response together with the local pathology report (please refer to the pathology manual). Local assessment should include the result of the pathology re-staging, margin and lymph node assessment (plus cytology if applicable).

For central assessment, the percentage of residual viable tumour that was identified on routine hematoxylin and eosin staining will be evaluated. Patients with tumours with 10% or less residual viable tumour tissue in lung primary tumour after neoadjuvant treatment at the time of resection will be considered to have had an MPR. Refer to the blinded independent central review (BICR) Pathology Charter for further assessment details.

Patients with no residual viable tumour cells in any of the specimens (primary tumours, lymph nodes and margins) will be considered to have had a pCR. Refer to the BICR Pathology Charter for further details.

The samples may also be used for exploratory research and diagnostic development (except in China and other selected countries and study sites, as per local regulations).

3.2 Tumour imaging assessments

Radiological tumour assessment from scans of the chest and abdomen (including the entire liver and both adrenal glands) using images (preferably) obtained via CT with IV contrast, will be performed according to local practice. Tumour assessments of the brain will also be performed at screening and at disease recurrence for all patients, using images from contrast-enhanced MRI (preferred over CT) at disease recurrence for patient's in the EFS follow-up period.

A baseline scan should be collected during the screening period (D-28 to D-1; see study CSP SoA Table 1 Screening period) for disease staging and for use as a baseline for the post-neoadjuvant treatment/pre-surgery scan. Scans obtained per the patient's CSP SoC prior to randomisation do not need to be repeated and are acceptable to use as neoadjuvant baseline evaluations if the criteria outlined in the CSP paragraph 8.1.2.1 are met. A pre-surgery tumour assessment scan should subsequently be performed upon completion of neoadjuvant study therapy, at the pre-surgical assessment visit (D64[-1 to +21 days]; see study CSP SoA Table 1 Surgery period).

Two whole body 18FDG-PET-CT scans will be performed: 1 scan at baseline, and 1 prior to surgery to allow the assessment of the exploratory endpoint of change in metabolic response in lesions of interest with PET Response Criteria in Solid Tumours (PERCIST) by BICR, and to assist with TNM (re)staging according to the investigator's judgement.

EFS follow-up period tumour assessments are then to occur according to the schedule outlined in study CSP SoA Table 2 (EFS follow-up and survival periods). For patients who underwent and completed surgery, a first post-surgical scan should be collected 24 weeks (±14 days) after surgery. It is likely that there will be no evidence of disease in the first post-surgical scan, and EFS follow-up scans will be evaluated exclusively for new lesions. Further scans should then be collected every 24 weeks until Week 264 (5 years) post-surgery, then every 48 weeks thereafter; or until disease occurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first). It is important to follow the scan schedule as closely as possible relative to date of surgery.

For patients entering the EFS follow-up period who did not undergo or complete surgery for reasons other than progression, the first EFS follow-up period scan should be performed 24 weeks (±14 days) after the last dose of neoadjuvant study therapy, then every 24 weeks until Week 264 (5 years), then every 48 weeks thereafter; or until disease progression, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first).

Patients will be determined to have an EFS event when the investigator identifies progression that precludes surgery OR on any scans performed during the EFS follow-up period.

If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not had an EFS event, every attempt should be made to resume subsequent assessments according to the original imaging visit schedule.

As a lesion later identified in a body part not scanned at baseline would be considered a new lesion representing disease recurrence, careful consideration should be given to the extent of imaging coverage at EFS follow-up baseline and at subsequent follow-up time points.

New or enlarging pleural effusions will be considered new equivocal lesions unless there are corresponding soft tissue changes suggestive of metastatic disease in which case they will be documented as new unequivocal lesions. Only significant and unequivocally new pleural effusions will be recorded as new unequivocal lesions and be indicative of disease recurrence.

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 previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the disease progression or recurrence date should be declared using the date of the initial scan when the new lesion first appeared.

New lesions will be categorised as local/regional recurrence, distant recurrence, or a new primary malignancy (either a second primary NSCLC or new malignancy other than NSCLC). When recurrence is first documented at any site, complete restaging is required to identify all sites of recurrence. Local or regional recurrence is defined as recurrence in the area of the tumour bed, hilum, or mediastinal lymph nodes. Loco-regional recurrence of the disease should be cytologically/histologically confirmed. Distant recurrence is defined as spread of disease beyond the area of the tumour bed, hilum, or mediastinal lymph nodes and can describe extrathoracic disease, metastasis to the contralateral lung, pleural metastasis, pleural effusion, or pericardial effusion. Distant recurrence should be diagnosed by radiological examination and/or histopathological confirmation if the metastatic lesion is easily accessible for biopsy.

Second primary NSCLC is defined as diagnosis of a new primary invasive NSCLC and should be pathologically or molecularly defined. A new cancer other than NSCLC is defined as diagnosis of a new malignancy excluding second primary NSCLC or recurrent NSCLC and should be pathologically defined as well. If the site is unsure whether a new lesion represents NSCLC recurrence, a second primary NSCLC, or a new malignancy, a tissue biopsy should be performed to characterise the nature of the new lesion. The development of a new cancer other than NSCLC should be regarded as an SAE. Please note that any new primary malignancy (either a new primary invasive NSCLC or new malignancy other than NSCLC), confirmed by pathology if clinically feasible, is not considered an EFS event or DFS event.

All images will be collected on an ongoing basis and sent to an AstraZeneca-appointed CRO for quality control and storage for blinded independent central reads (BICR), if required. Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from the sites to the CRO (rather than courier transfer) is strongly encouraged. If performed, results of these independent reviews will not be communicated to Investigators, and results of Investigator tumour assessments will not be shared with the central reviewers. The management of patients will be based (in part) upon the results of the tumour assessments conducted by the Investigator and not by BICR.

3.3 Efficacy Variables

3.3.1 Primary end point: Major pathological response (MPR)

The primary endpoint of MPR is defined as ≤ 10% viable cancer cells in the surgical specimen, as assessed per central pathology laboratory post-surgery. Patients will only be considered to have an MPR if they also have an R0 margin result. Details of how the pathology data are collected and analysed, using both the IASLC and Chemotherapy methods, are specified in the Pathology Charter version 2.0 (dated as 05Dec2022).

IASLC method will be considered as the primary method and the chemotherapy method will be considered as secondary technique for assessment of pathological response.

As described in the Pathology Charter version 2.0, the central pathologists will determine the MPR status for each patient using both methods. The central pathology laboratory will indicate in the data transfer whether adjudication or round-table discussion has been required as described in the Pathology Charter and will flag the final central pathology result.

For reporting and analysis purposes, patients will only be considered to have an MPR if they also have an R0 margin result i.e. overall MPR result will be programmatically derived whereby only those patients who are deemed to have a ≤ 10% viable cancer cells in the surgical specimen by central pathological assessment and have R0 (from PATHREP CRF) will be classed as having an MPR.

"Not evaluable of MPR" will be summarised in 2 categories, to include;

- Patients who are not evaluable per central pathology assessment or who do not have a surgical specimen will be captured as "non-evaluable" or "missing," as appropriate.
- Patients with a R1/R2 margin result or those without a margin result (from PATHREP CRF).

Patients without a response of MPR by central pathological assessment (corresponding to evaluable viable cancer cells >10%) and those who are not evaluable of MPR will be considered as non-MPR.

This interim analysis of MPR will occur when approximately half of the patients randomised have had the opportunity to complete surgery and an MPR assessment. The final analysis of MPR will occur when the last randomised patient has had the opportunity to complete surgery and the MPR assessment.

3.3.2 Pathological complete response (pCR)

Pathological complete response (pCR) is defined as absence of any viable cancer cells in the dissected tumour samples, including the main tumour, lymph nodes, and margins as assessed per central pathology laboratory post-surgery. The process followed by the central pathology laboratory will be same as that used for MPR analysis.

Patients will only be considered to have pCR if they also have an R0 margin result i.e. overall pCR result will be derived programmatically whereby only those patients who are deemed to have pCR by central pathology laboratory and have R0 (from PATHREP CRF) will be classed as having pCR.

"Not evaluable of pCR" will be summarised in 2 categories;

- Patients who are not evaluable per central pathology assessment or who do not have a surgical specimen will not be considered as having a pCR will be captured as "non-evaluable" or "missing," as appropriate.
- Patients with a R1/R2 margin result or those without a margin result (from PATHREP CRF).

Patients without a response of pCR by central pathological assessment (corresponding to evaluable viable cancer cells > 0%) and those who are not evaluable of pCR will be considered as non-pCR.

pCR will be evaluated at the final MPR analysis.

3.3.3 Nodal Downstaging

Nodal downstaging is assessed in accordance with the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system. Pathology nodal downstaging (based on local pathology review) is defined as baseline N2 patients becoming N1/N0 or N1 to N0 at the time of surgery. Nodal downstaging assessment will only be formally assessed for patients with pathological staging available at both timepoints (baseline (crf page PATHGOM) and time of surgery (crf page PSTAG1). Patients who do not have baseline staging, patients who do not have a surgical specimen, or whose surgery was incomplete, will not be considered as having downstaging and will be labelled as "not applicable".

Downstaging, stable, and upstaging is tabulated as in Table 4:

Table 4 Baseline stage vs post-neotreatment stage

Baseline stage	**Post-neotreatment stage (Pathological Staging)**				
	N0	N1	N2	N3	No surgical specimen/ surgery not complete
N0	stable	upstaging	upstaging	upstaging	NA
N1	downstaging	stable	upstaging	upstaging	NA
N2	downstaging	downstaging	stable	upstaging	NA
No baseline	NA	NA	NA	NA	NA

Patients with NA results will not be included in the analysis.

Downstaging will be evaluated at the final MPR analysis.

3.3.4 Event free survival (EFS)

EFS is the key secondary endpoint and is defined as the time from the date of randomisation until an event occurs (ie, date of event or censoring - date of randomisation +1). An event is defined as the first of the following:

- Documented disease progression that precludes surgery or prevents completion of definitive surgery
- Recurrence or a new lesion, local or distant post-surgery. A new primary malignancy confirmed by pathology, if clinically feasible, is not considered an EFS event
- Patients who did not undergo surgery for reasons other than disease progression, documented PD after the neoadjuvant period
- Death due to any cause (event date is the date of death)
- Discovery upon attempting surgery that the surgery cannot be completed due to progresssion (event date is the date of the first attempt at surgery)

After completion of the neoadjuvant period, patients who do not undergo or complete definitive surgery for reasons other than progression will continue to be followed in the EFS follow-up period and will be determined to have an EFS event when the investigator identifies disease progression on any subsequent radiological imaging.

Any patient without an event at the time of analysis will be censored based on the last recorded date on which the patient was known without an event (censoring details are specified in Section 4.2.6).

The interim analysis for EFS will occur at the same time of the MPR final analysis. The final EFS analysis will be conducted when all patients have had the opportunity for at least 3 years follow-up post-surgery or post the last dose of neoadjuvant study treatment**,** i.e. 42 months after the last patient randomised.

3.3.5 Disease free survival (DFS)

DFS will only be evaluated on the resected analysis set (RAS). DFS is defined as the time from the date of surgery until the first date of disease recurrence (local or distant) or date of death due to any cause (in the absence of recurrence), whichever occurs first.

Pathological confirmation from biopsied lesions, if performed according to investigators' judgement and local practice, will also be taken into consideration (as applicable). A new primary malignancy confirmed by pathology, if clinically feasible, is not considered a DFS event.

Patients who did not have an event at the time of analysis will be censored at the latest date of post-surgical scans.

DFS will be evaluated at the same timepoints as EFS, and at the same time point of final OS analysis (approximately 5.5 years after the last patient is randomised).

3.3.6 Overall survival (OS)

OS is defined as the time from the date of randomisation until death due to any cause (i.e. date of death or censoring – date of randomisation + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF). Patients will be followed up to approximately 5.5 years after the last patient is randomised to allow

opportunity for all patients to be followed up 5 years post-surgery or post the last dose of neoadjuvant study treatment.

Survival calls will be made in the 1 week following the date of DCO for each analysis timepoint where OS will be assessed. If the death date is after the data cut-off date, these patients will be censored at the date of the data cut-off. Death dates may be found by checking publicly available death registries where it is possible to do so under applicable local laws to obtain a current survival status.

For any OS analysis performed at IDMC or where OS is not pre-planned to be analysed, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE module is only completed for patients off treatment if a survival sweep is not performed). The last date for each individual patient is defined as the latest among the following dates (Note: complete dates without imputation) recorded on the case report forms (CRFs):

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Tumour imaging assessment date
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF

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. If the death year/month is later after the last date known to be alive, then the death date will be imputed as:

a. For Missing day only – using the 1st of the month
b. 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, i.e. censored at the last known alive date.

3.3.7 PERCIST response

PERCIST response assessed by BICR will have 5 categories: complete metabolic response, partial metabolic response, stable metabolic disease, progressive metabolic disease, and NA.

3.3.8 Cure rate

The cure rate is defined as the percentage of patients in the study who are still alive and disease free for a certain period of time after they finished the surgery.

The 5-year landmark cure rate will be calculated as the disease-free survival rate at 5 years post surgery, at the same time as final OS analysis.

3.4 Clinical outcome assessments

Patients will perform the PRO assessments using an electronic tablet (ePRO) at day 1 of each cycle and treatment discontinuation visit in the neoadjuvant period, at pre-surgical assessment in Surgery period, at the AstraZeneca-supplied adjuvant osimertinib treatment decision visit , Week 12, Week 24, and Q24 weeks until Week 264 post-surgery then every 48 weeks (± 14 days), or until disease recurrence, withdrawal of consent, or death in EFS follow-up period, as indicated in the study CSP SoA (Table 1 and Table 2). The following PRO instruments will be administered in this study (see study CSP Appendix F).

3.4.1 EORTC QLQ-C30 and EORTC QLQ-LC13

Symptoms and overall quality of life will be assessed using EORTC QLQ-C30 and QLQ-LC13.

The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population that was developed by the EORTC Quality of Life Group 1993. It consists of 30 questions that can be combined to produce 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), 5 functional scales (physical, role, cognitive, emotional, and social), and a global measure of health status/QoL.

Each subscale, with the number of questionnaire item(s) and item range is shown in Table 5.

Table 5 EORTC QLQ-C30 Scoring version 3.0

	Subscale name	Individual Questionnaire	Number of Items	Item Range
Functioning scales	Physical functioning (PF2)	1 - 5	5	3
	Role functioning (RF2)	6, 7	2	3
	Cognitive functioning (CF)	20, 25	2	3
	Emotional functioning (EF)	21 - 24	4	3
	Social functioning (SF)	26 - 27	2	3
Symptom scales	Fatigue (FA)	10, 12, 18	3	3
	Pain (PA)	9, 19	2	3
	Nausea/vomiting (NV)	14, 15	2	3
Individual items	Dyspnea (DY)	8	1	3
	Insomnia (SL)	11	1	3
	Appetite loss (AP)	13	1	3
	Constipation (CO)	16	1	3

	Subscale name	Individual Questionnaire	Number of Items	Item Range
	Diarrhea (DI)	17	1	3
Global Health Status/quality of life (GHS/QoL)		29, 30	2	6
Financial difficulties (FI)		28	1	3

The EORTC QLQ-LC13 is a lung-cancer specific module measuring lung cancer-associated symptoms and side effects from conventional chemotherapy and radiotherapy, comprising 13 questions to assess cough, haemoptysis, dysphagia, site specific pain, sore mouth, dyspnoea, peripheral neuropathy, alopecia and pain medication (Bergman et al 1994). With the exception of a multi-item scale for dyspnoea, all are single items (Table 6).

Table 6 EORTC QLQ-LC13 Scoring

	Subscale name	Individual Questionnaire	Number of Items	Item Range
Lung cancer symptoms	Coughing (LCCO)	1	1	3
	Haemoptysis (LCHA)	2	1	3
	Dysphagia (LCDS)	7	1	3
	Pain in arm or shoulder (LCPA)	11	1	3
	Pain in other parts (LCPO)	12	1	3
	Pain in chest (LCPC)	10	1	3
Treatment-related symptoms	Sore mouth (LCSM)	6	1	3
	Dyspnoea (LCDY)	3,4,5	3	3
	Peripheral neuropathy (LCPN)	8	1	3
	Alopecia (LCHR)	9	1	3

For both EORTC QLQ-C30 and QLQLC13, an outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales and the global health status/quality of life (GHS/QoL) scale, according to the EORTC QLQ-C30 Scoring Manual and QLQ-LC13 instructions, respectively.

The principle for scoring these scales is the same in all cases:

- Step 1: Estimate the average of the items that contribute to the scale; this is the raw score, calculated as $RawScore = RS = (I_4 + I_2 + \ldots + I_n)/n$ where I_n is the score of non-missing individual item n.
- Step 2: Use a linear transformation to standardise the raw score, so that scores range from 0 to 100:

  QLQ-C30 Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

QLQ-C30 Symptom scales / single items / QLQ-LC13 scales: $S = \{\frac{(RS-1)}{range}\} \times 100$

QLQ-C30 GHS / QoL: $S = \{\frac{(RS-1)}{range}\} \times 100$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 and QLQ-LC13 have been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the GHS / QoL, which are 7-point questions with range = 6.

QLQ-C30 higher scores on the GHS/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity; higher scores on QLQ-LC13 represents greater symptom severity.

Changes in score compared with baseline will be evaluated in the neoadjuvant treatment period. For each subscale, if < 50% of the subscale items are missing, then the subscale score will be calculated based on non-missing items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing.

The primary PRO measures of interest are EORTC QLQ-C30 GHS/QoL, physical functioning, symptoms of fatigue and appetite loss, and EORTC QLQ-LC13 symptoms of dyspnoea, cough and chest pain.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically relevant change is defined as a change in the score from baseline of ≥ 10 for scales/items from the QLQ-C30 and the QLQ-LC13 (Obosa et al 1998). For example, a clinically relevant deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline (defined as Day 1, pre-dose) of ≥ 10. A clinically relevant improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥ 10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsening as shown in Table 7. Patients with no baseline data will be excluded from any change from baseline analyses.

Table 7 Mean change and assessment response in symptoms and health-related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-LC13/QLQ-C30 symptom scales/items	≥ +10	Worsening
	≤ -10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales GHS/QoL	≥ +10	Improvement
	≤ -10	Worsening

Score	Change from baseline	Visit response
	Otherwise	No change

3.4.2 EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions.

For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions.

The EQ-5D profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the EQ-5D-5L profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population and the base case will be the UK perspective. Where a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm (Van Hout et al. 2012).

In addition to the descriptive system, respondents will also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

The evaluable population will comprise a subset of the FAS who have a baseline EQ-5D-5L assessment.

3.4.3 Compliance

Compliance and evaluability rate will be calculated for separately for QLQ-C30 and QLQ-LC13:

Compliance rate = number of evaluable forms/number of expected forms × 100

Evaluability rate = number of evaluable forms/number of received forms × 100

- An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, i.e., a questionnaire from a patient who has not died, has not lost follow-up or withdrawn from the study at the scheduled assessment time, excluding patients in countries with no available translation.

- An evaluable form = a questionnaire with a completion date and at least 1 subscale that is non-missing.
- A received form = a questionnaire that has been received and has a completion date and at least 1 individual item completed.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable questionnaire at the time point, divided by number of patients still expected to complete questionnaires. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable questionnaires, divided by the number of received questionnaires.

3.5 Health Care Resource Use Variables

To investigate the impact of treatment and disease on health care resource, the following variables will be captured:

- Type of hospital attendances
- Primary sign or symptom for hospital visit
- Length of hospital stay
- Length of any time spent in an intensive care unit (ICU)

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalisation or start of study drug if the start of study drug is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalisation. The length of ICU stay will be calculated using the same method.

3.6 Safety Variables

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs, ECG, LVEF, and ECOG performance status.

3.6.1 Exposure and dose modifications

3.6.1.1 Neoadjuvant period

Exposure of Osimertinib/Placebo

Duration of exposure is defined as follows:

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

- Total (intended) exposure (days) = (min(last dose date where dose > 0 mg in neoadjuvant period, date of death) – first dose date +1)

Actual exposure time (days) will be calculated from first dose to the last dose, taking account of dose interruptions

- 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 total and actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Exposure of chemotherapy (Pemetrexed, Cisplatin, and Carboplatin)

Duration of treatment on chemotherapy will be in terms of the number of cycles and total exposure, for each chemotherapy study drug and overall chemotherapy.

A cycle corresponds to a period of 21 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if chemotherapy is started, even if the full dose is not delivered.

The total exposure (days) will be calculated as the (min(last dose date where dose > 0 mg for any of Pemetrexed, Cisplatin, and Carboplatin, date of death) – first dose date + 21) .

Missed or forgotten doses

Missed and forgotten doses should be recorded on the DOSE module as a dose interruption with the reason recorded as "Patient 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.

Patients who permanently discontinue during a dose interruption

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.

3.6.1.2 EFS follow-up period

Duration of exposure (months) of AstraZeneca-supplied adjuvant osimertinib in EFS follow-up period is defined as the (min(last dose date where dose > 0 mg in EFS follow-up period, date of withdrawal of consent, date of death, date of DCO) – first dose date in EFS follow-up period +1) / 30.4375.

EFS follow-up safety follow-up

EFS follow-up safety follow-up is defined as 28-days after the last dose of last study treatment in EFS follow-up period.

- EFS follow-up Safety Follow-up = min(last dose date in EFS follow-up period +28, date of starting a subsequent anti-cancer therapy, date of withdrawal of consent, date of death, date of DCO) – first dose date +1

3.6.2 Adverse events (AEs)

AEs (including SAEs) in neoadjuvant period will be collected for all patients from the time of signature of the screening ICF for the study until 28-days after the last dose of neoadjuvant treatment for patients who do not undergo surgery, or 90-days post-surgery) but prior to the next treatment.

Any AE with an onset date after the completion of the neoadjuvant safety follow-up period (as defined above), that is considered to be possibly related to one of more study drugs (or study procedures) should be reported as an AE or SAE, as applicable. SAEs assessed as possibly related to optimal care medication in the EFS follow-up phase (non-IMPs) should be reported via local pharmacovigilance procedures.

For patients receiving AstraZeneca-supplied adjuvant osimertinib in the EFS follow-up period of the study, SAEs and AESIs will be collected at the first EFS follow-up treatment visit, the Week 12 visit, the Week 24 visit, and subsequently every 12 weeks (±14 days) for 3 years; at treatment discontinuation, and at safety follow-up (28 days after the last dose of AstraZeneca-supplied adjuvant osimertinib).

Neoadjuvant period treatment emergent adverse event (TEAE) is defined as AEs with onset, or worsen (by investigator report of a change in intensity), from the date of first dose up to and including 28 days after last dose of IP but prior to the next treatment. A treatment related AE will be considered as treatment emergent regardless the AE onset date.

EFS follow-up period TEAE is defined as AEs with onset, or worsen (by investigator report of a change in intensity), from the date of first dose of AstraZeneca-supplied adjuvant osimertinib up to and including 28 days after last dose of AstraZeneca-supplied adjuvant osimertinib but prior to the subsequent anti-cancer therapy treatment. A treatment related AE will be considered as treatment emergent regardless the AE onset date.

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A SAE is an AE occurring during any study phase (including treatment and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above

Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report (CSR). A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these maybe marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

AEs of special interest

AEs of special interest (AESIs) represent pre-specified AEs that are considered to be of importance or particular interest to a clinical development program. The AESIs for the study including but not limited to Interstitial lung disease (ILD) (including pneumonitis), Haematological Toxicities, Cardiac failure, and Wound Healing. The final AESIs will be identified before the clinical database lock (CDL).

These AESIs have been identified as a list of categories provided by the patient safety team. Preferred terms used to identify adverse events of special interest will be listed before database lock and documented in the Study Master File. Groupings of certain MedDRA preferred terms will be based on preferred terms provided by the medical team and a listing of the preferred terms in each grouping will be produced.

Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to database lock (DBL) to ensure any further terms not already included are captured within the categories.

3.6.3 Analysis of Total Calcium per NCI CTCAE criteria

Corrected calcium records will be programmatically derived from Total Calcium and Albumin and appended to the lab dataset for grading.

Corrected Calcium = serum calcium + 0.8 × (4 - serum albumin)

3.6.4 Laboratory Safety Variables

The following laboratory variables (Table 8) will be summarised:

Table 8 Laboratory safety variables

Hematology(whole blood)	Clinical Chemistry(Serum/ Plasma)	Urinalysis (Urine)
Haemoglobin (Hb)	Albumin	Glucose
Red Blood Cell (RBC) count	Alanine transaminase (ALT)[b]	Protein
Hematocrit	Aspartate transaminase (AST)[b]	Blood
Reticulocytes	Alkaline phosphatise (ALP)[b]	
Leukocyte count	Bilirubin, total[b]	
Leukocyte differential count (absolute count)[a]	Blood creatinine	
- Neutrophils	Calcium, total	
- Lymphocytes	Corrected Calcium	
- Monocytes	Blood creatine phosphokinase [f]	
- Basophils	Creatinine Clearance[c]	
- Eosinophils	Cystatin C [f]	
Platelet count	Glucose	
	Lactate dehydrogenase (LDH)[d]	
	Magnesium	
	Potassium	
	Sodium	
	Urea/Blood Urea Nitrogen[e]	

[a] The value is to be provided as percentage of the leukocyte count if the absolute leukocyte differential counts are not available.
[b] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × ULN (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[c] Creatinine clearance will be derived by the Investigator using the method of Cockcroft and Gault (Cockcroft & Gault, 1976), using actual body weight or assessed by 24-hour urine creatinine.
[d] LDH is an additional variable collected during screening only.
[e] Depending on local practice.
[f] CPK and cystatin C are required in patients randomised after local approval of CSP v3.

3.6.5 Vital Signs

Vital signs will include temperature, systolic and diastolic blood pressure, weight, pulse rate, and respiratory rate.

3.6.6 Electrocardiograms (ECG)

The average of triple ECG results (heart rate, PR, QRS, QT, and QTcF intervals) at each timepoint will be derived for the analysis.

3.6.7 Pulmonary function tests

Pulmonary function testing includes FEV1 and DLCO.

3.6.8 ECOG performance status

Performance status will be assessed at the scheduled visits indicated in CSP schedule of assessments (SoA) table according to WHO criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.

2 = Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled, cannot carryon self-care, totally confined to bed or chair.

3.6.9 Left ventricular ejection fraction (LVEF)

An echocardiogram or Multi Gated Acquisition Scan (MUGA) scan to assess LVEF will be performed at the visits indicated in CSP SoA.

The modality of the cardiac function assessments must be consistent within a patient; i.e., 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.

3.6.10 Covid-19 test

Participants will be tested for Covid-19 as clinically indicated and in accordance with local procedures. If available, nucleic acid and/or IgM/G tests will be performed.

3.7 Pharmacokinetic Variables

Plasma samples for pharmacokinetic assessments will be collected as per the study CSP SoA (neoadjuvant period). Samples will be analysed by Covance BioA Laboratory , on behalf of AstraZeneca.

Pharmacokinetics analysis of the plasma concentration data for osimertinib, and its metabolites AZ5104 will be performed by Clinical Pharmacology Quantitative Pharmacology, AstraZeneca or delegate on behalf of Clinical Pharmacology Quantitative Pharmacology. The actual sampling times will be used in the parameter calculations.

The ratio of metabolite to osimertinib will be calculated. The plasma concentration data for osimertinib and metabolites will also be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allows.

The data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods. A separate analysis plan will be written to describe these analyses. The results of any such analyses will be reported separately from the CSR.

Where possible the appropriate PK parameters will also be determined for the metabolites of osimertinib.

4. ANALYSIS METHODS

4.1 General Principles

4.1.1 Populations for analyses

Efficacy (except DFS) and PRO data will be summarised and analysed based upon the FAS. The resected analysis set (RAS) will be used for DFS endpoint. Safety and treatment exposure data will be summarised based upon the safety analysis set. Study population and demographics and baseline disease characterists will be summarised based upon the FAS.

4.1.2 General principles

The below mentioned general principles will be followed:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm. Overall totals will be calculated for baseline summaries only.
- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- SAS® version 9.3 (or higher) will be used for all analyses.

A month is operationally defined to be 30.4375 days. One year is defined to be 365.25 days.

Data will be presented in data listings by patient identifier and treatment arm.

Where analysis models are stratified by the randomisation stratification factors, the strata obtained in IRT at randomisation will be used, not the values recorded in the electronic case report form (eCRF).

4.1.3 Baseline definition and post baseline summaries

In neoadjuvant treatment period, for efficacy the last observed measurement prior to randomisation will be considered the baseline measurement. However, if an evaluable assessment is only available after randomisation but before or on the first dose of randomised treatment then this assessment will be used as baseline. Last PRO assessments (EORTC QLQ-C30, EORTC QLQLC13 and EQ-5D-5L) on or prior to cycle 1 day 1 will be considered as baseline for PRO analysis and summaries.

For safety endpoints the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. The average of triplicate ECG results at the last assessment before the first dose will be considered as the baseline. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

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.

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.

In EFS follow-up period, the last assessment just prior to the surgery will be considered as the baseline for safety summaries.

4.1.4 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 variable.

Missing safety data will generally not be imputed unless otherwise stated. However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification) or "> x" (i.e. 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.

Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

4.1.4.1 Imputation of partial dates

Should the whole date be missing it is more difficult to follow a general principle and these should be reviewed within the study and decided how to be handled.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not advised to be used to calculate durations where the results would be less accurate.

- For missing initial diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.

- For missing concomitant medication, and AE start dates, the following will be applied:
  a. Missing day - impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date
  b. Missing day and month - impute 1st January unless year is the same as first dose date then impute first dose date
  c. Completely missing - impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date
- For missing concomitant medication, and AE end dates, the following will be applied:
  a. Missing day - impute the last day of the month
  b. Missing day and month - impute 31st December.

Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

- Partial death date imputation rule is specified in Section 3.3.6 Overall survival (OS) .

4.1.4.2 Imputation rules for lab values outside of quantification range

Lab values below the lower limit of quantification (LLoQ) that are reported as "< LLoQ" or "≤ LLoQ" in the database will be imputed by LLoQ × 0.99 for analysis purposes. The original value will be listed.

Lab values above the upper level of quantification (ULoQ) that are reported as "> ULoQ" or "≥ ULoQ" in the database will be imputed by ULoQ × 1.01 for analysis purposes. The original value will be listed.

4.2 Analysis Methods

Efficacy analysis (including PRO) will be performed to compare osimertinib as monotherapy versus chemotherapy alone (Arm 3 versus Arm 1), and to compare osimertinib in combination with chemotherapy versus chemotherapy alone (Arm 2 versus Arm 1). No comparison between Arm 3 and Arm 2 will be made.

Table 9 is a summary of statistical methods to be conducted for study primary and secondary endpoints. If one of two treatment arms (Arm 2 & Arm 3) is dropped at MPR interim analysis, other efficacy endpoints will not be analysed for the comparison between that treatment arm with Arm 1. Only the MPR and pCR summaries will be reported for this treatment arm afterwards.

Table 9 Statistical analyses methodology

Endpoints Analysed	Analysis / Analysis set
MPR	CMH test /FAS
	Subgroup Analysis /FAS

Endpoints Analysed	Analysis / Analysis set
pCR	CMH test /FAS
Downstaging	CMH test /FAS
EFS	Stratified log-rank test /FAS Subgroup Analysis /FAS
DFS	Stratified log-rank test /RAS
OS	Stratified log-rank test /FAS
EORTC QLQ-C30 and EORTC QLQ-LC13	MMRM for PRO change from baseline /FAS

Table 10 is the planned analysis time for efficacy endpoints.

Table 10 Efficacy analyses time

	MPR interim	MPR final	EFS final	OS final
MPR	X	X		
pCR		X		
Downstaging		X		
EFS		X*	X	
OS		X	X	X
Cure rate			X	X
DFS		X	X	X
EFS vs MPR exploratory		X	X	
EFS vs Downstaging exploratory		X	X	

* Interim analysis for the EFS.

4.2.1 Multiplicity

A multiple testing procedure will define which significance levels will be applied to the interpretation of the raw p-values for the primary endpoint of MPR and secondary endpoint EFS in the osimertinib plus chemotherapy (combo) arm versus the chemotherapy plus placebo (control) arm, and in the osimertinib (mono) arm versus the control arm. The family-wise error rate is strongly controlled at 4.998% (two-sided) for these endpoints (0.002% alpha has been spent in MPR interim analysis).

The test procedure is described as: MPR for combo versus control is first tested at alpha = 4.998%.

If this test is not statistically significant, the test procedure stops and no null hypothesis is rejected. If the test is significant ($p<0.04998$), then alpha=4.998% is recycled and distributed

with 4.898% for EFS test on combo versus control, and 0.1% for MPR test on mono versus control. If the EFS test on combo versus control is significant, the corresponding alpha can be further recycled to EFS test on mono versus control. If the EFS test on combo versus control is not significant, the procedure will stop.

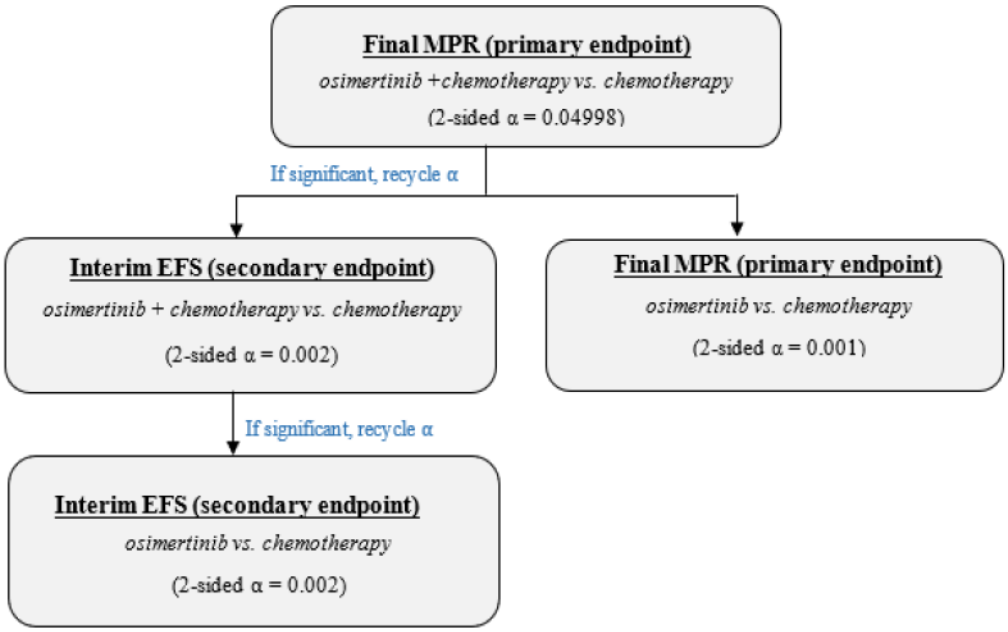
Since two analyses of MPR are planned, the Haybittle-Peto (Haybittle 1971, Peto et al 1976) boundary approach will be used to maintain an overall 2-sided 4.998% type I error with 0.001% alpha spent on each treatment arm compared with control at an interim analysis.

As 2 analyses of EFS are planned, the Haybittle-Peto boundary approach will be used to maintain an overall 2-sided 4.898% type I error with 0.2% alpha spent on the EFS interim analysis and the remaining alpha spent at the final EFS analysis to control overall 2-sided 4.898% type I error. The final analysis of EFS will be conducted when all patients have had the opportunity for at least 3 years follow-up post-surgery. The hierarchical testing procedure will be followed for final EFS test by testing EFS on combo versus control first and if significant, the alpha will be fully recycled to EFS test on mono versus control. The exact 2-sided alpha will be calculated based the exact information fraction at the time of the analysis. Alpha will be fully exhausted.

The significance level for the MPR analyses will be calculated using the statistical software package EAST® by specifying the information fraction of 0.5 for the interim analysis and 1.0 for the final analysis. The information fraction will be calculated based on the exact number of patients finished the surgery at the analysis time-point divided by the total number of patients at the final analysis time-point (N=234).

The multiple testing procedure (as shown in Figure 2) will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint of MPR in the combo arm versus control and the MPR in the mono arm versus control intended for label claims.

Figure 2 Multiple testing procedure



EFS, Event-free survival; MPR, major pathological response; vs, versus

4.2.2 Time-to-event endpoint considerations

Log-rank and Cox

Time-to-event data (EFS, DFS, and OS) will be analysed using a log-rank test stratified by stage, mutation type and race.

The log-rank test will be stratified according to the values recorded in the randomisation system, as the analysis is then consistent with the possible permutations of the randomisation.

A Cox proportional hazards model containing treatment and the stratification factors alone will be used to estimate time to event endpoints' (EFS and DFS) HRs to ensure that output from the Cox model is likely to be consistent with the results of using the stratified log-rank test.

Handling of ties

Efron approach will be used to handle ties in Cox proportional model.

Hazard ratio and confidence interval estimation

If there are too few events available for a meaningful analysis of a particular subgroup category/level (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup category/level and the time to event endpoint will not be analysed. In this case, only descriptive summaries will be provided.

If the resulting strata are too small (i.e., < 20 events) the strata will be collapsed in the following pre-defined order to allow analysis. The China cohort strata will be collapsed first (to Asian vs. Non-Asian), followed mutation type, and finally disease stage.

The treatment difference measured by HR and 100*(1-alpha)% CI will be obtained directly from the U and V statistics (Berry et al 1991), e.g. 95% CI will be calculated as below:

$$HR = exp\left(\frac{U}{V}\right)$$

$$95\%\ CI\ for\ HR = \left(exp\left\{\frac{U}{V} - \frac{1.96}{\sqrt{V}}\right\}, exp\left\{\frac{U}{V} + \frac{1.96}{\sqrt{V}}\right\}\right)$$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki} - e_{1ki})$ is the stratified log-rank test statistic (with d_{1ki} and e_{1ki}, the observed and expected events in group 1, stratum k) and $\sqrt{V} = \sqrt{\sum_k V_k}$ is the standard deviation of the log-rank test statistic obtained from the LIFETEST procedure with a STRATA term for each stratification variable.

P-value will be obtained from the stratified log-rank test.

EFS, DFS and OS data will be analysed using the same methodology.

Proportionality assumption

The assumption of proportionality will be assessed for EFS, DFS and OS. In the event of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up.

Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-ln(time) interaction term) to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect can be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found this may be a result of a treatment-by-covariate interaction, which will be investigated.

4.2.3 Primary endpoint: Major Pathological Response (MPR)

Primary analysis MPR will be calculated as number of patients with MPR response in the full analysis set (FAS) (ie, all randomised patients). A sensitivity analysis will be conducted excluding patients with MPR "non-evaluable" from the denominator. The analysis of MPR will be performed using the Cochran-Mantel-Haenszel (CMH) test, stratified by disease stage (Stage II versus Stage III), race (Non-Asian, Other Asian [excluding Chinese living in China] and Chinese living in China), and mutation type (Ex19del versus L858R). The treatment effect will be estimated by the odds ratio together with its corresponding 100*(1-alpha)% CI and p-value (refer to significant level in Section 4.2.1).

The number and percentage of MPR responders and non-responders will be summarized along with a supportive summary of the number and percentage of patients with R0, R1 and R2 margin status post-surgery. Waterfall plots with each patient's percentage of regression in tumor area with viable cells (percentage of residual viable tumor-100%) and a table summarizing the residual viable tumor by randomized treatment group will be provided.

The analysis of MPR will be performed for the MPR assessed by both IASLC method and the chemotherapy method.

4.2.4 Pathological Complete Response (pCR)

The pCR will be analysed similarly to the primary endpoint MPR, using the CMH test, stratified by disease stage, race and mutation type. The treatment effect will be measured by the odds ratio together with the 95% CI.

The number and percentage of PCR responders and non-responders will be summarized along with a supportive summary of the number and percentage of patients with R0, R1 and R2 margin status post-surgery. Waterfall plots with each patient's percentage of regression in tumor area with viable cells (percentage of residual viable tumor-100%) will be provided.

The number and percentage of pCR responders and non-responders will be summarized by treatment arm.

A sensitivity analysis will be conducted excluding patients with pCR "non-evaluable" from the denominator. The analysis of pCR will be performed for both IASLC method and the chemotherapy method.

The analysis of pCR will take place at the final MPR analysis.

4.2.5 Nodal Downstaging

The analysis of pathological nodal downstaging (the proportion of patients with downstaging) will be analysed using the CMH test, stratified by disease stage, race and mutation type. The treatment effect will be measured by the odds ratio together with 95% CI.

The analysis for nodal downstaging is based on a subset of the FAS containing patients with baseline pathological staging N1 or N2. In addition, subgroup analyses will be performed in patients with baseline pathological staging N2 and in patients with baseline pathological staging N1, respectively.

A baseline stage versus post-neotreatment stage cross table,with number of patients (%) downstaging, stable, and upstaging (defined in Table 4), will be presented for pathological staging.

The analysis of pathological nodal downstaging will take place at the final MPR analysis.

4.2.6 Event free survival (EFS)

The number (%) of patients with the event or censoring will be summarised for each of the situations as listed in Table 11.

Table 11 Event and censoring for EFS

Situation	Event or Censored	Event Date/ Censored Date
(No baseline or no post-baseline assessment), and no surgery, didn't die and did not progress *	C	Randomisation Date (Study day 1) (if no corresponding assessment dates in PFSSURG, DISREC, and ASMPERF/1 crf pages or surgery date)
No documented disease progression, death due to any cause before surgery or death due to any cause after surgery without two consecutive missed visits	E	Death Date
No documented disease recurrence, death due to any cause after surgery, immediately after two or more consecutive missed visits	C	Date of last assessment or surgery date (last date in DISREC, and ASMPERF/1 crf pages, and surgery date) before missed two consecutive visits
Disease progression that precludes surgery	E	Date of progression (assessment date in PFSSURG crf page)
Attempting surgery that the surgery cannot be completed due to disease progression	E	The date of the first attempt at surgery
Recurrence or a new lesion, local or distant without two consecutive missed visits	E	Date of recurrence or date of documented new lesion (assessment date in DISREC crf page)
Recurrence or a new lesion, local or distant after surgery, immediately after two or more consecutive missed visits	C	Date last assessment or surgery date (last date in DISREC and ASMPERF/1 crf pages, and surgery date) before missed two consecutive visits
Documented disease progression after Neoadjuvant period (for patients who did not undergo surgery due to reasons other than disease progression)	E	Date of progression (DISREC/PFSSURG crf page)
Documented disease progression after surgery (for patients who did not complete surgery due to reasons other than disease progression)	E	Date of progression (DISREC crf page)
No documented disease progression and alive at the time of analysis	C	Last assessment date or surgery date (last assessment date in DISRECand ASMPERF/1 crf pages and surgery date)

* crf ASMPERF page for baseline; crf ASMPERF1 and DISREC pages for post baseline.

If a patient doesn't have an efficacy assessment post-surgery and dies within 40 weeks (12 weeks + 24 weeks + 4 weeks window) after the date of surgery, the death date will be considered as an event.

Definition of two missed visits

If the previous efficacy assessment is before the surgery, then two missed visits will equate to 40 weeks (12 weeks + 24 weeks + 4 weeks window) after the date of surgery. For patients entering the EFS follow-up period who did not (undergo or complete) surgery due to reasons other than progression, the 12-week visit will be calculated from the last day of neoadjuvant treatment.

If the previous efficacy assessment is at or after post-surgery week 12 then two missed visits will be equate to 52 weeks since the previous assessment, allowing for early and late visits (48 weeks + 4 weeks window).

Please note that NE will not be considered as a missing visit.

The analysis for EFS will be performed using the log-rank test stratified by stage, mutation type and race. P-value from the stratified log-rank test and the treatment difference measured by a HR and 100*(1-alpha)% CI will be presented. Analysis method details were specified in section 4.2.2.

A Kaplan-Meier (K-M) curve, K-M estimates for median EFS along with the corresponding 2-sided 95% confidence intervals (CIs) will be presented by treatment arm.

The final EFS analysis will be conducted when all patients have had the opportunity for at least 3 years follow-up post-surgery, i.e. 42 months after the last patient randomised.

The study is not designed or powered for testing the treatment difference in EFS.

Subgroup analyses will be conducted comparing EFS in the subgroups defined by the 3 stratification factors: disease stage, race and mutation type. Details see section 4.2.10.

EFS sensitivity analyses

Evaluation-time bias

EFS sensitivity analysis adjusting for evaluation-time bias will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression/death and the previous evaluable efficacy assessment will be analysed using a stratified log-rank test, as described for the primary analysis of EFS.

Table 12 Change of censoring rule for EFS evaluation-time bias sensitivity

Situation	Event or Censored	Event Date/ Censored Date
Disease progression/recurrence or death due to any cause after surgery or during EFS follow-up period if	C	The midpoint between the time of progression and the previous efficacy assessment, or between the time of

Situation	Event or Censored	Event Date/ Censored Date
didn't have a (definitive) surgery due to reasons other than PD, immediately after missed two consecutive visits		progression and the randomisation date if no post-baseline assessments.

Ascertainment bias

If BICR-assessed EFS based on CT/MRI scans is provided, a sentivity analysis for the ascertainment bias will be conducted based on the BICR data. The stratified log rank test will be repeated on EFS using the BICR data. A summary table will be produced to present the discrepancy between the Investigator assessment and BICR assessment, including the proportion of patients with Investigator assessed disease progression but no BICR progression will be summarized, and vice versa.

4.2.7 Disease free survival (DFS)

DFS will be evauated on the resected Analysis Set (RAS).

The number (%) of patients with a DFS event or censoring will be summarised as in Table 13.

Table 13 Event and censoring for DFS

Situation	Event or Censored	Event Date/ Censored Date
No documented disease recurrence, death due to any cause	E	Death Date
Death after two or more consecutive missed visits	C	Date of death before missed two consecutive visit
Disease recurrence (local or distant) without two consecutive missed visits	E	Date of disease recurrence
Disease recurrence (local or distant) after two or more consecutive missed visits	C	Date of last assessment before two consecutive missed visits
No documented disease recurrence and alive at the time of analysis	C	Latest date of evaluable disease assessment after the surgical date on which the patient was known to be alive and event free

Patients who develop a new primary invasive NSCLC or a new malignancy, which is not NSCLC, will continue to be followed for DFS-defined events.

The time window of missing two consecutive visits (after the date of surgery) is the same as EFS.

DFS data will be analysed using the same methodology and model as for the analysis of EFS, provided there are sufficient events [≥ 20 events (disease recurrence or death (by any cause in the absence of recurrence)) across Arm 3 and Arm 1, or across Arm 2 and Arm 1] available for a meaningful analysis; otherwise, descriptive summaries will be provided.

No subgroup analysis will be performed for DFS.

No statistical testing of DFS will be conducted.

4.2.8 Overall survival (OS)

OS data will be analysed using the same methodology as for the analysis of EFS and a 5-year landmark analysis will also be conducted, provided there are sufficient events (≥ 20 deaths across Arm 3 and Arm 1, or across Arm 2 and Arm 1) available for a meaningful analysis; otherwise, descriptive summaries will be provided.

The final OS analysis data cut-off will occur 5.5 years after the last patient has been randomised or all patients have died, whichever occurs first.

No statistical testing of OS will be conducted.

4.2.9 Subgroup analyses for primary endpoint MPR

In addition to the analysis of MPR described in section 4.2.3, the following subgroup analyses will be conducted by comparing MPR between the experimental arm (either Arm 2 or Arm 3) and the control arm (Arm 1):

- Disease Stage (Stage II versus Stage III) from IVRS
- Race (Chinese/Asian, non-Chinese/Asian, non-Asian) from IVRS
- EGFR mutation type (Exon 19 Deletion or L858R) from IVRS
- Central plasma ctDNA EGFR (Ex19Del and L858R) mutation status at screening (positive for either Ex19Del or L858R, negative for both, unknown)
- Age group (<65 yrs vs >=65 yrs)
- Sex (Male vs Female)
- Smoking history (yes vs no)
- ECOG WHO Performance score.

The odds ratio and the response rate difference with corresponding 95% CIs will be calculated (e.g. using CMH option in SAS® procedure FREQ) for each level of above listed subgroups.

These response rate difference at each level of subgroups and the associated two-sided 95% CIs will be presented on forest plots (one plot for one comparison), along with the results of the overall primary MPR analysis and the results of MPR analysis with no adjustment of stratification factors.

The MPR in a subgroup less than 10 responders (across Arm 3 and Arm 1, or across Arm 2 and Arm 1) will not be analysed. In this case, only descriptive summaries will be provided.

No adjustment to the significance level for testing will be made since the subgroup analysis may only be supportive of the primary analysis of MPR.

Quantitative interaction

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit (likelihood ratio test for the binary data (MPR) accounting for the change in degrees-of-freedom) of a logistic regression model including treatment, strafication factors, and all strafication factors by treatment interaction terms, with one that excludes the interaction terms and will be assessed at the two-sided 10% significance level. If the fit of the model is not significantly improved (i.e. not statistically significant), then it will be concluded that overall, the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process, all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail, M. & Simon, R., 1985).

4.2.10 Subgroup analyses for secondary endpoints EFS and pCR

Subgroup analyses will be performed to compare EFS between treatment arms (i.e., using a Cox-Proportional Hazards Model), by same subgroups listed in primary MPR subgroup analysis in section 4.2.9.

For each subgroup, the HR and 95% CI will be calculated from a single Cox proportional hazards model that contains a term for treatment, the subgroup covariate of interest and the treatment by subgroup interaction term. The treatment effect HR will be obtained for each level of the subgroup from this model. The Cox models will be fitted using SAS® PROC PHREG with the Efron approach for handling ties.

These HRs and associated two-sided 95% CIs will be summarised and presented on forest plots (one plot for one comparison), along with the overall EFS results (EFS analysis in section 4.2.6 and section 4.2.2). In addition, a Cox proportional hazards model that contains a term for treatment arm will be fitted and the treatment effect HR and the two-sided 95% CIs will also be included in the subgroup forest plots.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events per level in

a subgroup), the analysis for the EFS in that subgroup will not be conducted. In this case, only descriptive summaries will be provided.

If there are sufficient patients with pCR (e.g. 10 responders across 2 treatment arms for comparison), subgroup analyses of pCR will be conducted in order to explore the consistency of the treatment effect across the subgroups. The analysis method and subgroups are described in Section 4.2.9.

4.2.11 Comparison of baseline tumour EGFR mutation status

The following comparisons will be conducted for baseline tumour EGFR mutation status:

- Tumour DNA vs plasma ctDNA (central tissue test results will be used as the reference where available, otherwise the local test results which were used to confirm study eligibility will be used)
- Local vs central EGFR mutation test (central tissue test results will be used as reference)

Cross summary table (as Table 14) will be produced for tumour DNA vs plasma ctDNA, and local vs central EGFR mutation, respectively.

Table 14 Format for reporting results comparing a new test outcome to the reference standard outcome

		Reference standard (Tumour DNA / Central results)		
		Positive	Negative	Total
New tests (Plasma ctDNA / Local results)	Positive	TP	FP	RM^1
	Negative	FN	TN	RM^2
Total		CM^1	CM^2	N_{all}
TP=number of true positive events; FP=number of false positive events; TN=number of true negative events; FN=number of false negative events; CM =column marginal; RM=row marginal				

Baseline EGFR mutation status will be compared between tumour DNA and plasma ctDNA. Analysis will be carried out separately for each sensitizing mutation, Ex19Del and L858R, and as well as in aggregate. Analysis will be in all screened subjects with evaluable results from neoadjuvant baseline plasma samples. The central lab tissue test results will be used where available, otherwise the local results which were used to confirm the study eligibility will be used as reference.

The baseline tumour EGFR mutation status will also be compared between the local results (results used to confirm the study eligibility) and central tissue test results in subjects with evaluable results from neoadjuvant baseline tumour samples. Analysis will be carried out separately for each sensitizing mutation, Ex19Del and L858R, and as well as in aggregate.

The following measures of agreement will be calculated for comparisons described above: the overall percent agreement (OPA); the percentages of total subjects where the new tests and the reference standard agree. This will be calculated from Table 14 in the following way:

- Overall percent agreement (OPA) = 100% * (TP+TN) /(N_{all})
- Positive percent agreement (PPA) = 100%* TP/(TP+FN)
- Negative percent agreement (NPA) = 100% * TN/(FP+TN)

The overall agreement will always lie somewhere between positive percent agreement and the negative percent agreement.

The predictive value of a positive results (PPV) i.e. the proportion of test positive subjects who have the target condition and predictive value of negative result (NPV) i.e. the proportion of test negative subjects who do not have target condition, will also be calculated:

- PPV=100% * TP/(TP+FP)
- NPV=100% * TN/(TN+FN)

4.2.12 PERCIST response

The summary of PERCIST response (complete metabolic response, partial metabolic response, stable metabolic disease, and progressive metabolic disease) will be based on the FAS who completed FDG PET scans at the baseline and pre-surgical visits.

The number (%) of patients of each PERCIST response category (complete metabolic response, partial metabolic response, stable metabolic disease, progressive metabolic disease, or not available) will be summarised by treatment arm.

No statistical testing will be conducted.

A cross table (like Table 15) will be produced to explore the relationship between the PERCIST response and the pathological response (achieved MPR and not achieved MPR).

Table 15 PERCIST response versus pathological response

			Pathological response	
			Achieved MPR	Not Achieved MPR
PERCIST assessment	Responder	Complete metabolic response	n_{11}	n_{12}
		Partial metabolic response		
	Non-responder	Stable metabolic disease	n_{21}	n_{22}
		Progressive metabolic disease		
		No PERCIST response or not evaluable		

The odds ratio is calculated as odds of patients achieving MPR response in the patients who are PERCIST responders divided by the odds of patients achieving MPR response in the patients who are PERCIST non-responders, i.e.

$$OR = \frac{(n_{11})/n_{12}}{(n_{21})/n_{22}}$$

The corresponding 95% CI for the odds ratio will be calculated and presented.

4.2.13 Cure rate

The 5-year landmark cure rate will be presented as the DFS KM survival rate estimates at 5 year by treatment arm at the same time as final OS analysis.

4.2.14 Additional exploratory analysis

No p-value will be calculated for the following additional exploratory analyses.

4.2.14.1 Explore the association between MPR and EFS

EFS will be compared between patients with and without MPR, within each treatment group by stratified log-rank test with the same stratification factors as primary endpoint. The hazard ratio (HRs) and associated 95% confidence interval (CI) will be obtained directly from the U and V estimator. No p-value will be calculated . The Kapan-Meier plot of EFS will be presented by MPR status within each treatment group. The total number of EFS events and median EFS (calculated from KM plot, with two sided 95% CIs) and other landmark Kaplan-Meier estimates of EFS by MPR status will be provided.

A sensitivity analysis may be conducted to exclude subjects with MPR non-evaluable from the MPR response 'No' group if the proportion of those subjects are greater than 5% of overall population across arms.

Further exploratory analysis to evaluate the association of EFS with pathological assessment of %RVT will be considered, e.g.

- Expore the correlation between EFS and %RVT as a continuous variable: Scatter plot of %RVT against EFS will be produced. If the scatter plot suggests a relationship between the EFS and %RVT, further analysis may be conducted.
- Explore the association between EFS and the pathological response defined by different thresholds of %RVT. Such as MPR defined by a threshold of 10% RVT, additional subgroups of patients can be formed by using different cut-point of %RVT, for example, using 20%, 30%, etc, The exploratory analysis for the association between MPR and EFS may be repeated for the pathological response defined by different thresholds of %RVT.

4.2.14.2 Explore the association between staging status and EFS

Further exploratory analysis will be conducted to assess the association between EFS and a subjects staging status. Following surgery, a subjects staging status will be updated and after comparing with baseline staging status, they will be categorized as either stable, upstage or downstage in a summary table. The downstaging group will be used as reference group and compared with stable stage and upstage group separately.

Similarly as exploratory analysis of EFS with MPR, we will explore EFS with upstage, downstage and stable groups, within each treatment group, by log-rank test. The HRs and 95% CI obtained by U and V estimator will be reported (the downstage group will be used as reference group). The KM plot comparing upstage, downstage and stable groups will be presented. The total number of EFS events and median EFS (calculated from KM plot, with two sided 95% CIs) and other landmark Kaplan-Meier estimates of EFS by downstage, upstage or stable stage will be provided as well.

4.2.14.3 Subgroup analyses of MPR, pCR and EFS by EGFR mutation confirmation methods at randomisation

To evaluvate clinical efficacy in the patients who are randomised by fine needle aspiration (FNA) tissue test EGFR mutation results subgroup analyses of efficacy endpoints of MPR, pCR and EFS for these patients randomised by tumor tisue biopsy and FNA will be performed if there are succificent patients who are randomised based on their FNA sample results, e.g. at least 30 patients across 3 treatment arms.

For MPR and pCR, the same methodology and model as for the subgroup analysis of MPR (Section 4.2.9) will be utilized. The odds ratio with its corresponding 95% CI for each subgroup will be presented. For EFS, the same methodology and model as for the subgroup analysis of EFS (Section 4.2.10) will be used. The HR and 95% CI for each subgroup will be presented.

4.2.15 Subsequent Therapy

Subsequent ant-cancer therapy medicaions will be coded using the WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes. Subsequent anti-cancer therapies received after discontinuation of study neoadjuvant treatment but prior to the first dose of AstraZeneca-supplied adjuvant osimertinib and received during the EFS follow-up period will be summarised respectively by treatment group. Given post-operative radiation therapy is not a mandated study procedure but is optional per investigator discretion, it is not considered as a subsequent therapy on this study, and will be summarised in a separate table.

4.2.16 Surgery

Surgery data collected in CRF page SURG will be summarized for:

- Subjects who underwent the surgery
- Subjects who completed the surgery
- Subjects who didn't undergo the surgery, along with reasons
- Subjects who didn't complete the planned surgery, along with reasons
- Subjects had the surgery within 91 days after the first neoadjuvant dose, along with reasons if not
- Days from the last neoadjuvant dose date to the surgery
- Days from the surgery to the first dose date of receiving AstraZeneca-supplied adjuvant osimertinib

- Duration of surgery
- Resection types
- Blood loss and blood transfusion

All surgery data will be presented in a listing.

4.2.17 Disease recurrence

Disease recurrence data recorded in eCRF will be summarised by treatment arm and presented in a listing.

4.2.18 Patient reported outcomes (PROs)

The analysis population for PRO data will be the FAS. Details of the analysis visit window for PRO assessments is specified in section 4.3.1.2.

QLQ-C30 and QLQ-LC13

Mixed models repeated measures (MMRM) of change from baseline in primary PRO measures of interest in the neoadjuvant period

Change from baseline in the primary PRO scores for cough, dyspnoea, chest pain, fatigue, appetite loss, physical function and GHS/QoL will be analysed separately for each treatment comparison using a mixed model for repeated measures (MMRM). The analysis will be to compare the average treatment effect from the randomisation to the pre-surgical visit (or to the disease progression before the surgery).

PRO assessments during neoadjuvant period will be mapped to analysis visit based on the analysis visit window specified in section 4.3.1.2. If there are two or more values potentially allocated to the same scheduled assessment, the post baseline assessment closest to the scheduled assessment date will be included in the summaries and in the MMRM.

The MMRM model will include patient, treatment, visit, and treatment-by-visit interaction as explanatory variables, baseline PRO score as a covariate along with the baseline PRO score by visit interaction. Treatment, visit, and treatment-by-visit interaction will be fixed effects in the model; patient will be included as a random effect. Restricted maximum likelihood (REML) estimation will be used. Adjusted mean estimates will be derived that will estimate the average treatment effect over assessments giving each visit equal weight.

For this overall treatment comparison, adjusted mean estimates per treatment arm and corresponding 95% CIs will be presented along with an estimate of the treatment difference and 95% CI. No p-values will be presented. The treatment-by-visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-patient error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample code for implementing the MMRM analysis:

```
proc mixed data=PRO method = reml;
        class TRT(ref="SoC") VISIT SUBJECT;
```

```
model PROSC = TRT VISIT TRT*VISIT PROBL PROBL*VISIT /s ddfm=kr;
repeated VISIT / type=UN patient=SUBJECT;
lsmeans TRT / at means diff alpha=0.05 cl;
run;
```

where TRT is the randomised treatment, VISIT is the analysis visit, PROSC is the change from baseline in the PRO score, and PROBL is the baseline PRO score.

For the estimation of TRT*VISIT means an additional model will be run using all visits and the following lsmeans statement:

```
lsmeans TRT*VISIT / slice=VISIT diff alpha=0.05 cl;
```

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. If there are still issues with the fit of the model or estimation of the treatment effects, SUBJECT will be treated as a fixed effect.

Change from baseline, summary scores and compliance

Scores from PRO instruments (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L [EQ-5D index score and VAS score]) will be summarised using change from baseline and categories of change (Worse, Improvement, No change defined in Section 3.4.1), presented separately for neoadjuvant period and EFS follow-up period.

One summary will be produced for neoadjuvant analysis visits (cycle 2 day 1, cycle 3 day 1, pre-surgery visit) using the last assessment on or prior to the neoadjuvant cycle 1 day 1 as the baseline.

For the EFS follow-up period, a second summary will be produced for subjects with EFS follow-up period visits, using the last assessment on or prior to the neoadjuvant cycle 1 day 1 as the baseline.

All PRO data will be listed.

PRO (QLQ-C30, QLQ-LC13 and EQ-5D-5L) compliance rate will be summarised by timepoint for neoadjuvant period and EFS follow-up period respectively.

To support submissions to payers, additional analyses may be undertaken and these will be outlined in a separate Payer Analysis Plan (PAP) for PROs.

4.2.19 Biomarker analysis – Exploratory Analysis

Biomarker analysis will be reported in separate documents.

4.2.20 Health care resource use

Descriptive statistics (as appropriate, including means, median, ranges or frequencies and percentages) will be provided for each randomised treatment arm on the different types of hospital admissions, the length of stay of people admitted in to hospital for at least one overnight stay and length of stay of people admitted to intensive care / high dependency units, as well as the primary sign or symptom the patient presents with.

To support submissions to payers, additional analyses may be undertaken and these will be outlined in a separate Payer Analysis Plan.

4.2.21 Data cut-offs

There are 4 planned data cut-offs (DCOs) for this study consisting of an interim analysis for futility (DCO1) of the primary endpoint (MPR), a final analysis for the primary endpoint (DCO2), a final analysis for the key secondary endpoint of EFS (DCO3) and an overall survival (OS) final analysis (DCO4). Refer to Table 10 for the further details.

At analysis for EFS, DFS, or OS, a survival sweep should be performed within 7 days after each DCO to ensure that complete overall survival data is collected, updating the survive and death raw data to ensure the most accurate EFS, DFS and OS analyses possible.

4.3 Safety and Demographics

4.3.1 Safety

4.3.1.1 Analysis period for safety

Neoadjuvant analysis period is from the first dose to the minimum of (date of last dose in neoadjuvant period + 28 days, the next treatment start date – 1, date of withdrawal of consent, date of death). The next treatment includes EFS follow-up AZ supplied adjuvant osimertinib treatment or other subsequent anti-cancer therapy after the last dose of the study treatment in neoadjuvant period.

EFS follow-up analysis period is from the date of first dose of AstraZeneca-supplied adjuvant osimertinib in EFS follow-up period to the minimum of (last dose date of AstraZeneca-supplied adjuvant osimertinib in EFS follow-up period + 28 days, date of starting a subsequent anti-cancer therapy, date of withdrawal of consent, date of death, date of DCO). EFS follow-up analysis period will not be defined for patients didn't have a surgery due to disease progression.

Unless otherwise specified, safety summaries will be presented by analysis period.

4.3.1.2 General considerations for safety and PRO assessments

Vital signs, laboratory data, ECG, and PRO assessments during the neoadjuvant period will be assigned to calculated visit windows (using the first study dose date as the reference date in the calculation of study day). Time windows is defined for any presentations that summarise values by visit. The following conventions will apply:

- The time windows will be exhaustive so that data recorded at any time point during the neoadjuvant period has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- All unscheduled visit data before the pre-surgical visit during neoadjuvant period have the potential to be included in the summaries. Unscheduled safety assessments after the pre-surgical but before the surgery will not be mapped to an analysis visit, therefore will not be included in the neoadjuvant analysis period visit based summaries. All efficacy data will be included in efficacy analysis.

- The analysis window for the visits following baseline will follow the visit window specified in CSP SoA Table 1 be constructed in such a way that the upper limit of the interval falls half way 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 1 day.
- Analysis visit window for vital signs, laboratory data, ECGs, ECOG, and PRO assessments in neoadjuvant analysis period (Note additional assessments are introduced in Japan sites)

Analysis Period	Visit Name	Normal Visit Study Day	Visit Window(Study Day)
Neoadjuvant	Cycle 1 Day 1	Day 1	1
	Cycle 2 Day 1	Day 22	(2, 32)
	Cycle 3 Day 1	Day 43	(33, one day prior to Pre-surgical assessment, or day 63 for patients not entered into Surgery period)
	Pre-surgical	Day 64	As eCRF collected pre-surgical visit
	Cycle 4 (Not applicable for PRO)	Day 64	As eCRF collected cycle 4 visit

- Analysis visit window for vital signs, laboratory data, ECGs, ECOG, and PRO assessments in neoadjuvant analysis period (Japan)

Analysis Period	Visit Name	Normal Visit Study Day	Visit Window(Study Day)
Neoadjuvant	Cycle 1 Day 1	Day 1	1
	Cycle 1 Day 8	Day 8	(2,11)
	Cycle 1 Day 15	Day 15	(12,18)
	Cycle 2 Day 1	Day 22	(19, 25)
	Cycle 2 Day 8	Day 29	(26, 36)
	Cycle 3 Day 1	Day 43	(37, 50)
	Cycle 3 Day 15	Day 57	(51, one day prior to Pre-surgical assessment, or day 63 for patients not entered into Surgery period)
	Pre-surgical	Day 64	As eCRF collected pre-surgical visit
	Cycle 4 (Not applicable for PRO)	Day 64	As eCRF collected cycle 4 visit

- For visit based summaries in neoadjuvant analysis period:
  - If there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarised, or the earlier non-missing observation, in the event the values are equidistant from the nominal visit date (if assessment time is not recorded for one of the values, the average of observations equidistant to the nominal visit study day will be used for analysis/summaries).
  - The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment arm, visit data will only be summarised if the number of observations is greater than the minimum of 10 patients dosed.
    - 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 summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

Baseline for safety and PRO assessments:

- For safety assessments baseline will generally be the last value obtained prior to the first dose of study medication except triplicate ECGs.
- The baseline of ECG will be the mean of triplicate ECGs at the last timepoint prior to the first dose.
- Last PRO assessment on or prior to cycle 1 day 1 will be used for baseline.
- If two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average will be taken as a baseline value.
- For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative.
- In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline.
- Where safety data are summarised over time, study day will be calculated in relation to date of first treatment.

– The date of randomisation will be used as a reference date for PRO study day.

Safety assessments and PRO data during the EFS follow-up analysis period will be summarised and presented separately by CRF collected visits for patients receiving AstraZeneca-supplied adjuvant osimertinib during EFS follow-up analysis period.

4.3.1.3 Adverse events (AEs)

Neoadjuvant analysis period

All AEs onset in the neoadjuvant analysis period, both in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and CTCAE grade, will be listed and summarised descriptively by count (n) and percentage (%) for each treatment arm. Latest available MedDRA version will be used for coding. Missing coding terms should be listed and summarised as "Not coded".

Any AE occurring or worsening on or after the first dose date and within 28 days of discontinuation of IP , but before the start of next treatment, will be included in TEAE summaries.

All AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of CTCAE grade and relationship to study drug. Frequencies and percentages of patients reporting each preferred term will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries).

Summary information (the number and percent of patients by treatment) by System organ class (SOC) and preferred term (PT) will be tabulated for:

- All AEs
- All AEs causally related to study medication
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to treatment
- AEs with outcome of death
- AEs with outcome of death causally related to treatment
- AEs leading to dose reduction and interruption (separately)
- All SAEs
- All SAEs causally related to study medication
- AEs leading to discontinuation of treatment
- AEs leading to discontinuation of treatment, causally related to treatment
- OAEs
- OAEs causally related to treatment
- AESIs

An overall TEAE summary of the number and percentage of patients in each category will be presented, as well as an overall summary of the number of events in each category. In addition, a truncated TEAE table of most common TEAEs, showing all events that occur in at

least 5% of patients overall will be summarised by preferred term, by decreasing frequency. This cut-off may be modified after review of the data.

AEs will be assigned CTCAE grades and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, PT and actual treatment arm. Fluctuations observed in CTCAE grades during study will be listed (where collected).

In addition, AEs with outcome of death, SAEs, AEs leading to discontinuation of treatment, AEs causally related to treatment, OAEs and AESIs will be listed.

Post Neoadjvant analysis period

AEs occurring or worsening on/after the min of (29 days post last dose of neoadjuvant treatment, the date of next anti-cancer therapy) and within 90 days post-surgery for subject who unerderwent the surgery will be reported for All AEs, SAEs, and AESIs.

Surgical related adverse events

AEs provoked by surgical resection (occurring or worsening on or after the date of surgery up to the min of (end of study, date of withdrawal of consent, data cut-off, death) will be summarized for:

- All surgical related AE
- All surgical related AE by maximum CTCAE grade
- Serious surgical related AE

EFS follow-up period

AEs onset in the EFS follow-up analysis period will be summarised separately for patients receiving AstraZeneca-supplied adjuvant osimertinib in the EFS follow-up period of the study.

Summary information (the number and percent of patients by treatment) by System organ class (SOC) and preferred term (PT) will be tabulated for:

- All SAEs
- AESIs

4.3.1.4 Adverse events of special interest (AESIs)

Preferred terms used to identify AESI will be listed before Clinical Database Locl (CDL) and documented in the Trial Master File. Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

An overall AESI summary of the above-mentioned grouped AE categories will include number (%) of patients who have:

- At least one AESI presented

- At least one AESI causally related to study medication
- At least one AESI leading to discontinuation of study medication

A summary of total duration (days) of AESI will be provided for events which have an end date and this may be supported by summaries of ongoing AESIs at death and, separately, at data cut-off.

Summary tables of AEs of special interest will be produced. The number (%) of patients experiencing any of the specified terms will be presented overall and by maximum CTCAE grade.

Additional summaries of time to onset of first AE for each grouped term and each preferred term within it; time to onset of first CTCAE grade three or higher and duration of AEs of special interest will be produced.

In addition, further summary tables from the AEs section listed above will be repeated for grouped AEs of special interest.

The number (%) of patients with AEs with a body system of Infections and Infestations occurring with concomitant low leukocyte/neutrophil counts (below the normal range) will be summarised. Only treatment-emergent events with an onset after the date of a treatment emergent low leukocyte/neutrophil count value, and before the date when the leukocyte/neutrophil value returns to normal, will be presented.

The above summary of AEs with a body system of Infections and Infestations will also be repeated for concomitant low neutrophil counts.

The number (%) of patients with AEs of bleeding occurring with concomitant low platelet counts (below the normal range) will be summarised. Bleeding adverse events will be identified using the "Haemorrhages" narrow MedDRA standardised MedDRA query (SMQ). Only treatment-emergent bleeding events with an onset after the date of a treatment-emergent low platelet count value, and before the date when the platelet value returns to normal, will be presented.

4.3.1.5 Death

A summary of deaths based on ITT population will be provided with number and percentage of patients, categorised as:

- Related to disease under investigation only
- AE outcome = death only
- Both related to disease under investigation and with AE outcome=death
- AE outcome = death only (AE start date > 28 days after last neoadjuvant treatment dose or after the start of next treatment)
- Other deaths (not captured in above categories)
- Patients with unknown/missing reason for death

Death within 30 days and with 90 days post-surgery will be summarized for patients who underwent the surgery.

A corresponding listing will be produced. Deaths in the EFS follow-up analysis period will be listed separately.

4.3.1.6 Laboratory evaluations

All laboratory data recorded in the eCRF will be listed.

If any additional analytes to those in Table 8 are also recorded then these will be listed only. All values will be classified as low (below range), normal (within range) and high (above range) based on project-specific reference ranges. As applicable, values will be converted to standard units and will be graded using the latest versions of CTCAE.

For clinical chemistry and haematology, shift tables will present movements from baseline to maximum or minimum (as applicable) according to reference range classification and CTCAE grade changes from baseline to the maximum grade on treatment will be provided. Corresponding shift tables ("Negative", "Trace", "Positive", "0", "+", "++", ">+++") will be produced for urinalysis.

A patient list for patients with potential Drug Induced Liver Injury (i.e. ALT or AST $\geq$ 3×ULN and TBIL $\geq$ 2×ULN, ALT or AST $\geq$ 5×ULN will be provided.

Liver biochemistry tests (ALT, AST, TBIL, ALP, GGT) results over time will also be presented graphically for patients with potential Drug Induced Liver Injury.

Plots of both the maximum post-baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) versus the maximum post-baseline total bilirubin, expressed as multiples of their upper limit of reference range will be produced.

Box plots of absolute values and change from baseline for all haematology and clinical chemistry parameters will also be presented.

Pregnancy testing results will be presented in a listing.

4.3.1.7 Vital signs and weight

Absolute values and change from baseline at each scheduled visit for pulse, BP and weight will be summarised by randomised treatment arm.

4.3.1.8 ECG

All ECG data received will be presented in data listings. The average of triplicate ECG results at the same timepoint will be used for the summaries. In case of missing one or two assessment(s) of triplicate ECGs, the average of available results will be used.

ECG summaries will be presented for patients in the safety analysis set. The following ECG parameters will be summarised (absolute values and change from baseline) by visit: QTcF, RR variability, PR interval, QRS complex, and QT interval.

Box plots for observed ECG parameters and change from baseline in ECG parameters over time will be presented.

Shift plots of the value corresponding to the maximum absolute change from baseline versus the baseline value for QTcF, with reference lines for 450 msec, ±30 msec and ± 60 msec change, will be presented.

QTc outliers are defined as QTcF values following dosing that are greater than 450 msec or are increases from baseline greater than 30 msec.

QTcF outliers will be highlighted in the data listings and summarised using the following categories:

- Values > 450 msec, > 480msec, > 500 msec
- Increase from baseline of > 30 msec, Increase from baseline of > 60 msec, Increase from baseline of > 90 msec
- Values > 450 msec and increases of > 30 msec, Values > 500 msec and increases of > 60 msec

The number and percentage of patients who meet the ECG outlier criteria at any assessment post-date of first dose will be summarised.

4.3.1.9 Left ventricular ejection fraction

Plots of absolute LVEF values and change from baseline in LVEF values at pre-surgical will be presented.

LVEF outliers for patients who have both baseline value and at least one post baseline assessment are defined as LVEF values (including unscheduled assessment) following dosing that are

- ≥10 percentage points (pp) decrease from baseline and < 50%, or
- ≥15 percentage points decrease from baseline and ≥ 50%.

The number of patients with the following LVEF values at each post-baseline scheduled LVEF visit, and the maximum post-baseline change will be displayed:

- LVEF increase
  - ≥ 30pp
  - ≥ 20 - < 30pp
  - ≥ 10 - < 20pp
- LVEF change < 10 percentage points (pp)
- LVEF decrease
  - ≥ 10 - < 20pp and absolute value < 50%
  - ≥ 10 - < 20pp and absolute value ≥ 50%
  - ≥ 20 - < 30pp and absolute value < 50%
  - ≥ 20 - < 30pp and absolute value ≥ 50%
  - ≥ 30pp and absolute value < 50%
  - ≥ 30pp and absolute value ≥ 50%

For the maximum change, patients with a maximum increase ≥ 10pp and a maximum decrease < 10pp will be summarised under their maximum increase, and patients with a maximum decrease ≥ 10pp and a maximum increase < 10pp will be summarised under their maximum decrease.

LVEF assessments in the EFS follow-up analysis period will be listed only.

4.3.1.10 ECOG performance status

ECOG performance status will be listed and summarised as frequency counts by visit and by treatment arm.

4.3.1.11 Liver diagnostic investigations and liver risk factors

Liver diagnostic investigation results and liver risk factors will be listed .

4.3.1.12 COVID-19

A listing of patients diagnosed with COVID-19, along with the COVID-19 testing results and treatment status (ongoing or discontinued the study treatment due to COVID-19) will be produced.

Depending on the extent of COVID-19 impact, summaries of delayed/missed visits, discontinuation of study treatment, discontinuation of study, and COVID-19 related protocol deviations may be generated.

4.3.2 Demographics and baseline characteristics

Demographics and baseline characteristics summaries will be based on the FAS.

The following will be summarised for all patients by randomised treatment arm:

- Patient disposition
- Important protocol deviations
- Inclusion in analysis sets
- Demographics (age, age group (<50, ≥ 50 and <65, ≥ 65 and <75, ≥ 75), sex, race and ethnicity)
- Patient characteristics at baseline (height, weight)
- Patient recruitment by country/region and centre
- Disease characteristics at study entry (primary tumour location, histology type, tumour grade, tumour invasions, AJCC stage, and clinical and mediastinal staging)
- EGFR mutation (Exon 19 Deletion or L858R)
- ECOG performance status (0, 1) at study entry
- Previous radiotherapy
- Previous chemotherapy prior to this study

- Medical history (past and current)
- Relevant surgical history
- Prior and concomitant medications
- Post-treatment anticancer therapy
- Post-treatment radiotherapy
- Nicotine use, categorised (never, current, former)

Disposition summaries will include the number and percentage of patients:

- Enrolled (informed consent received)
- Randomised
- Patients not randomised
- Included in each analysis set
- Patients ongoing study treatment (on neoadjuvant period) at the data cut-off
- Patients in each study period (Surgery period, EFS follow-up period, and Survival period) after discontinued or completed the neoadjuvant treatment.
- Patients who failed to undergo surgery, along with the reason surgery not done
- Patients who attempted to have a surgical resection, but failed to achieve complete resection

In addition, the number and percentage of patients who discontinued neoadjuvant treatment and who discontinued the study, including a breakdown of the primary reason for discontinuation will be presented.

The stratification information recorded in IVRS/IWRS versus data entered in CRF will be cross-tabulated to assess any mis-stratifications if there are discrepancies.

Medical history and relevant surgical history will be coded using the latest available MedDRA version. All medical history (past and current) will be listed and the number and percentage of patients with any medical history will be summarised by system organ class (SOC) and preferred term (PT). Relevant surgical history will be summarised similarly. All surgical history will be listed.

All important protocol deviations will be listed and summarised. All protocol deviations will be defined by the study team before database lock.

4.3.3 Concomitant therapies and other treatments

Prior medications, concomitant (including pre-medication of new therapy regimen) and post treatment medications summaries will be provided on the FAS.

Medications received prior to, concomitantly, or post-treatment will be coded using the WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes. Concomitant medications will be summarised by ATC classification codes.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 4.1.4.1.

Prior medications, concomitant and post treatment medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post-treatment medications are those with a start date after the last dose date of study treatment.

In addition, post-treatment anti-cancer medications will be summarised by randomised treatment arm.

The following summaries will be produced:

- Summary of prior medications
- Summary of concomitant medications
- Summary of post study treatment anti-cancer therapies during:
  - Post neoadjuvant treatment but prior to receiving the AstraZeneca-supplied adjuvant osimertinib
  - EFS follow-up period (after receiving the AstraZeneca-supplied adjuvant osimertinib)

More details for prohibited and restricted concomitant medications is specified in the study CSP Section 6.5.1.

All concomitant and other treatment data will be listed. Antiemetic therapies will be flagged in the listing.

Missing coding terms will be listed and summarised as "Not coded".

4.3.4 Exposure

Exposure will be summarised for the safety analysis set. The following summaries will be produced for neoadjuvant period:

- Summary of duration of exposure (including total exposure and actual exposure) of study treatment for osimertinib/matching placebo
- Summary of total exposure for chemotherapy

- Number of cycles chemotherapy received
- Number of cycles delayed in chemotherapy
- Summary of dosing interruptions and reductions for osimertinib/matching placebo
- Summary of dosing interruptions and reductions for chemotherapy (for cisplatin, carboplatin, and pemetrexed respectively)

The dosing administration of osimertinib/matching placebo), cisplatin, carboplatin, and pemetrexed will be listed by patient.

Duration (months) of AstraZeneca-supplied adjuvant osimertinib exposure during the EFS follow-up period will be summarised for patients who received AstraZeneca-supplied adjuvant osimertinib after the end of neoadjuvant treatment.

4.3.5 Pharmacokinetic data

Plasma concentrations of osimertinib and metabolite AZ5104 will be summarised by nominal sample time using standard summary statistics for PK concentrations (geometric mean, geometric coefficient of variation, geometric mean ± standard deviation, arithmetic mean, standard deviation, minimum, maximum and n) within each treatment arm. PK parameters will also be summarised within each treatment arm. All plasma concentrations and PK parameters will be listed regardless of whether they're excluded from summary statistics due to deviation (e.g. as a result of dose interruption, reduction or missing the dose before PK sample collection, or sampling time deviation, etc).

Outputs will display the data as described in the 'Reporting formats' tab of the PK Order Form spreadsheet.

5. IDMC AND INTERIM ANALYSES

Independent Data Monitoring Committee (IDMC) will be responsible for reviewing safety data throughout the conduct of the study, including one interim analysis for futility based on MPR: the smallest treatment effect of absolute difference of 6% when compared to the control arm, which will be performed once approximately half of all patients have had the opportunity to complete surgery and the MPR assessment per central pathology laboratory.

Independent data monitoring committee (IDMC)

An IDMC comprised of independent experts will be convened, and will meet to review unblinded safety data, initially approximately 6 months after the study has started or when a minimum of 20 patients have been randomised and have adequate follow up to complete the surgery (whichever is later). Three subsequent meetings will take place every 6 months and then meetings will be held yearly thereafter until completion of the primary analysis. Further meetings for review of safety data from all patients may be convened at the discretion of the IDMC. Following each meeting the IDMC will evaluate whether the trial should continue without change, be modified or stopped due to potential harm to patients.

Full details of the IDMC procedure and processes can be found in the IDMC Charter.

Interim analysis for futility

A small amount of alpha 0.001% (2-sided) will be assigned to the interim analysis for futility (under Haybittle-Peto boundary) for MPR testing on each experimental treatment arm against the control arm, respectively. This interim analysis will be conducted by the IDMC and a recommendation regarding continuing the study for each experimental treatment arm will be made to the sponsor.

One interim analysis is planned for the primary endpoint of MPR. This interim analysis will occur when approximately half of the patients have had the opportunity to complete surgery and the MPR assessment per central pathology labratory. The final analysis of MPR will occur when the last patient had the opportunity to complete surgery and the MPR assessment per central pathology laboratory, ie, approximately 6 months after the last patient is randomised at the alpha 4.998% (2-sided). This ensures an overall alpha of 5% across the interim and final anlaysis for the primary endpoint.

For the EFS endpoint, there is one interim analysis planned. The Haybittle-Peto boundary approach will be used to maintain an overall 2-sided 4.898% type I error with 0.2% alpha spent on the EFS interim analysis and the remaining alpha spent at the final analysis which will be conducted when all patients have had the opportunity for 3 years follow-up post-surgery (ie, 42 months after the last patient is randomised). The interim analysis for EFS will occur at the same time of the MPR final analysis.

The final analysis of EFS will be conducted when all patients have had the opportunity for at least 3 years follow-up post-surgery, i.e. 42 months after the last patient is randomised.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Additional exploratory analysis to explore the association between MPR and EFS, the association between staging status and EFS, and subsequent therapies will be performed (details see Section 4.2.14).

Time to deterioration for PRO subscales are not defined and will not be analyzed.

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8. DOCUMENT REVISION HISTORY

Version	Description of Update
2.0 (15JUN2023)	• Study object table (Section 1.1), added last exploratory objectives per CSP amendment. • Updated "Adjuvant period" to "EFS follow-up period" per the CSP amendment (entire document). • Modified resected analysis set definition (Section 2.1) . • Updated important protocol deviations wording (Section 2.2). • Added details for the primary endpoint (MPR) derivation (Section 3.3.1). • Added details for efficacy endpoint Nodal downstaging and EFS (Section 3.3.3 and 3.3.4) • Added Analysis window for Japan Sites (Section 4.3.1.2) • Added more details for MPR and pCR summaries/analysis (Section 4.2.3 and 4.2.4). • Specify the patients to be included in the planned interim analysis to reflect the CSP amendment (V3.0)
3.0 (Sept2024)	• Study object table (Section 1.1), added one more exploratory objective per CSP V5 amendment. • Edited protocol deviation (Section 2.2) • Deleted "Neoadjuvant safety follow-up" definition from Section 3.6.1.1 • Modified partial date imputation section (Section 4.1.4.1), no imputation for missing radiotherapy start date. • Modified EFS censoring rules (Section 4.2.6) • Added more subgroups for the subgroup analysis in Section 4.2.9 and Section 4.2.14.3 • Added quantitative interaction in Section 4.2.9 • Deleted Kappa coefficient (Section 4.2.11) • Added more details for the exploratory analysis for the association between MPR and EFS (Section 4.2.14.1 and Section 4.2.14.2) • Added subgroup analysis for MPR and pCR by EGFR mutation confirmation method at randomization (Section 4.2.14.3) • Added more detail for surgery data summaries (Section 4.2.16) • Updated the PRO baseline definition (Section 4.2.18) • Updated the analysis period definitions (TEAE during each analysis period) in Section 4.3.1.1 • Added AE post the Neoadjuvant analysis period (Section 4.3.1.3) • Added surgical related AE and SAE (Section 4.3.1.3) • Other edits (e.g. assessment schedule) to be consistent to CSP V5.0

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