Revised Clinical Study Protocol	
Drug Substance	Osimertinib (TAGRISSO™)
Study Code	D516AC00001
Version	5.0
Date	08 December 2023

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)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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Regulatory Agency Identifying Number(s): US IND 117879;
EU CT number: 2022-502606-33-00; EudraCT number: 2020-000058-89

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

CSP Version 5.0: 08 December 2023 Changes to the protocol are summarised below:

This non-substantial revision to the CSP v5.0 is adding the information for compliance with EU CTR.

The changes are described in detail below:

- Table 4: Updated to include IMP/AxMP classification
- Appendix A 4, (Data Protection): Updated to include the participant must be informed that data will be collected only for the business needs. The participant must be informed that data will be collected and in some cases their data may be pseudonymised. Included an additional section for personal data breaches to address EU CTR concerns relating to personal data breaches.
- Appendix A 6, (Dissemination of Clinical Study Data): Modify text to include that a description of this clinical study will be available on http://euclinical trials.eu/.
- Appendix I, (Country-Specific Requirements): Included a new appendix to capture all country-specific requirements previously covered in individual country protocols.

CSP Version 4.0: 05 July 2023 Changes to the protocol are summarised below:

This revision to the CSP v4.0 is adding the option of prospective central EGFR testing with available FFPE FNA sample using Idylla™ EGFR Mutation Test for patient selection in the NeoADAURA study (D516AC00001). Further updates include addition of SJS, TEN, and aplastic anaemia to Table 14 (Dose adjustment information for adverse reactions), TEN to Section 8.5.6.4 (Information on Specific Adverse Events) in line with current safety guidance, updates to clarify the evaluation of MPR and pCR in patients, updates to the EFS follow-up period evaluations, and updates to text describing when the final analysis of MPR and EFS will occur.

The changes are described in detail below:

- Section 1.1, (Synopsis): Updated the endpoint pCR definition to clarify “as assessed per central pathology laboratory”. Updated EFS evaluation text to include “or until approximately 5.5 years after the last patient is randomised”. Updated the statistical methodology text to clarify patients are only considered as having MPR if an R0 margin result is observed, and 2 new categories added to summarise those patients considered “Not evaluable for MPR”. Further updates to clarify the analysis of MPR.
- Section 1.3, (Schedule of assessments, Table 1): Changed “tumour FFPE tissue sample” to “tumour FFPE sample” to be inclusive of tumour tissue samples (eg, core needle biopsies) and FNA samples. Row for “Cytology FFPE sample for exploratory research (optional)” deleted, such that the sites can prioritise the FNA samples for the central EGFR testing by Idylla™ EGFR Mutation Test (including removal of corresponding footnote [z], and reordering of footnotes previously [aa], [bb], [cc], [dd], [ee], and [ff] to become footnotes [z], [aa], [bb], [cc], [dd], and [ee], respectively). Amended footnote (y) to include FNA sample collection and central testing by Idylla™ EGFR Mutation Test for patient selection in NeoADAURA when permitted by AstraZeneca. Added provision of additional tumour FFPE FNA samples, if available, for future confirmation testing using an FDA approved FNA test. Further clarify local Idylla™ EGFR testing results are not permitted for patient selection. Added

abbreviations for IFU and FNA to footnotes. Added assessments for Clinical chemistry, Haematology, and test Pregnancy at the C4 timepoint.

- Section 1.3, (Schedule of assessments, Table 2): Added abbreviation for FFPE to footnotes. Updates to footnotes [b] and [m] to add "or until approximately 5.5 years after the last patient is randomised". New row added for "Brain MRI (preferred) or CT" along with corresponding new footnote [u].
- Section 3: Deleted optional cytology sample for exploratory research so sites can prioritise the FNA samples for central EGFR testing.
- Section 3, (Table 3): Updated the endpoint pCR definition to clarify "as assessed per central pathology laboratory". Added exploratory objective to perform clinical efficacy analysis by tumour tissue versus FNA used for EGFR mutation confirmation at randomisation
- Section 4.1.1 and footnote ([1]): Changed text from "tumour biopsy" to "tumour sample" to be inclusive of both tumour tissue samples and FNA samples. Add collection of FNA sample per SoC when tumour biopsy is not available to footnote ([1]). Modify text to include FNA sample collection and central testing using Idylla™ EGFR Mutation Test for patient selection, when permitted by AstraZeneca. Further clarify local Idylla™ EGFR testing results are not permitted for patient selection.
- Section 4.1.4: Updated EFS evaluation text to include "or until approximately 5.5 years after the last patient is randomised".
- Section 6.3.1: Modified text to add collection of FNA samples for central testing using Idylla™ EGFR Mutation Test.
- Section 8.1.2.1: EFS follow-up period text updated to clarify that scans should happen until "disease recurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first)" in addition to the currently defined time points.
- Section 8.5.6.2: Table 14 updated to include dose modifications for SJS, TEN, and aplastic anaemia.
- Section 8.5.6.4.4: Updated to included TEN.
- Section 8.7.1: Changed "tissue" to "sample" to be inclusive of both tumour tissue samples and FNA samples. Add new footnote (f) to Table 18 to add the option of using FNA samples collected from SoC when tumour tissue sample is not available. Modify text for the collection of FNA samples.
- Section 8.7.1.1: Changed "tissue" to "tumour" to be inclusive of both tumour tissue samples and FNA samples. Modified text to allow FNA sample to be used for patient selection using Idylla™ EGFR Mutation Test when tissue biopsy sample is not available and permitted by AstraZeneca. Added provision of additional tumour FFPE FNA samples, if available, for future confirmation testing using an FDA approved FNA test. Further clarify local Idylla™ EGFR testing results are not permitted for patient selection.
- Section 8.7.1.2.1: Minor changes of "tissue" to "sample" to be inclusive of both tumour tissue samples and include FNA samples type; also clarified that detailed sample requirements will be included in the Laboratory Manual.
- Section 8.7.2: Deleted Cytology FFPE (exploratory analysis) row for "Screening" in Table 19 such that sites can prioritise the FNA samples for the central EGFR testing by the Idylla™ EGFR Mutation Test.
- Section 9.4.1.1: Text updated to clarify patients are only considered as having MPR if an R0 margin result is observed, and 2 new categories added to summarise those patients considered "Not evaluable for MPR". Further updates to clarify the analysis of MPR.
- Section 9.4.1.2: Text updated to clarify patients are only considered as having pCR if an R0 margin result is observed, and 2 new categories added to summarise those patients considered "Not evaluable for pCR".

- Section 9.4.1.3: Text stating when the final analysis of EFS will be conducted is moved, and the text "the study is not powered for testing the treatment difference in the EFS" is deleted.
- Section 9.4.4.3: Updated text to clarify that for the cure rate analysis, the DFS 5-year landmark will be calculated at the same time as the OS analysis.
- Section 9.5: Text modified to clarify when the final analysis of MPR will occur ("when the last patient has had the opportunity to complete surgery and the MPR assessment per central pathology laboratory"). Text modified to clarify when the final analysis of EFS will occur ("when all patients have had the opportunity for 3 years follow-up post-surgery [ie, 42 months after the last patient is randomised"]).
- Appendix I: Add abbreviation for FNA.

CSP Version 3.0: 10 January 2023 Changes to the protocol are summarised below:

The key revision to the CSP v3.0 is introducing the option for investigators to continue or reinitiate adjuvant osimertinib after Grade 1 or 2 ILD/Pneumonitis according to the toxicity management guidelines in Table 17, along with a new exploratory objective to explore ILD characteristics in such patients. In addition, the definition of EFS has been clarified, including the identification of EFS events in patients who do not undergo or complete surgery for reasons other than progression, and the Adjuvant Period has been renamed to EFS Follow-Up Period to better reflect the procedures performed and the patient population followed in this period, which includes patients who may or may not receive adjuvant treatment, but are still being followed for an EFS event.

The above and other changes are described in detail below:

Title page: CTIS number was added.

Synopsis (Intervention Groups and Duration): Instructions for EFS follow-up beyond 5 years were clarified (ie, Week 264 then every 48 weeks [±14 days]).

Section 1.3 (Schedule of assessments, Table 1): Pre-screening/Screening column split into 2 columns, new footnote (ee) added, and footnote (g) amended to clarify the timing of sample collections, procedures and the respective pre-screening/main ICF signing. Prior pulmonary function testing and ECHO/MUGA added to the list of assessments that may be used for screening purposes with consent of the patient, if performed within 6 weeks prior to randomisation. Timing of prior screening imaging results was also amended to 6 weeks prior to randomisation.

Section 1.3 (Schedule of assessments, Table 1): Text added to footnote (c) to clarify that for patients who complete 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.

Section 1.3 (Schedule of assessments, Table 1): Footnotes (f), (l), (w), and (bb) amended and a new footnote (dd) added to clarify the calculation of the corresponding cycles/days for procedures and assessments (independent of dosing delays or interruptions).

Section 1.3 (Schedule of assessments, Table 1): Clarification added to footnote (y) on sample collection and analysis in China.

Section 1.3 (Schedule of assessments, Table 1): New footnote (aa) added to clarify the samples that are optional for China (not to be collected and analysed until approved by relevant local authorities).

Section 1.3 (Schedule of assessments, Table 1): Clarification added in footnote (bb) regarding the need for 7 days of continuous dosing when referring to collection of the PK sample in all three treatment arms.

Section 1.3 (Schedule of assessments, Table 1): New row "HIV testing" and corresponding footnote (ff) added to outline screening for HIV in patients, and describe monitoring for patients with known HIV.

Section 1.3 (Schedule of assessments, Table 1): The requirement for pre-surgery pulmonary function tests was amended from mandatory to "as clinically indicated".

Section 1.3 (Schedule of assessments, Table 1): DLCO was removed from the pulmonary function testing row, but added to footnote (g) as a recommendation to include this assessment.

Section 1.3 (Schedule of assessments, Table 2): Column header for visit 1 revised to "Adjuvant IP-osimertinib treatment decision visit" to clarify the visit at which adjuvant osimertinib treatment is decided.

Section 1.3 (Schedule of assessments, Table 2): Instructions for EFS follow-up beyond 5 years were clarified (ie, Week 264 then every 48 weeks [±14 days]), and respective footnote (b) updated.

Section 1.3 (Schedule of assessments, Table 2): Cross-reference to Section 6.1.2.2 added to the final column of the "Osimertinib IP dispensing" row.

Section 1.3 (Schedule of assessments, Table 2): New row "HIV testing" and corresponding footnote (q) added to outline monitoring of patients with HIV.

Section 1.3 (Schedule of assessments, Table 2): New row added for additional tumour FFPE tissue collection for exploratory research at recurrence only, with reference to existing footnote (r; previously [o]) added to note this is not applicable in China, and footnote (s) added to note samples may be collected beyond the ±14 days' time window as long as the sample is collected prior to the start of the next anti-cancer therapy. Footnote (t) also added to clarify timing of collection of plasma sample for MRD/ctDNA analysis.

Section 1.3 (Schedule of assessments, Table 2): Footnote (a) revised to refer to Section 6.1.2.2 for AstraZeneca-supplied adjuvant osimertinib eligibility criteria.

Section 1.3 (Schedule of assessments, Table 2): Footnote (c) revised to clarify that patients without recurrence will continue to have EFS follow-up visits according to the schedule in Table 2.

Section 1.3 (Schedule of assessments, Table 2): Additional information added to Footnote (l) to clarify that in the EFS follow-up period scans do not need to be collected after the final EFS analysis.

Section 1.3 (Schedule of assessments, Table 2): Footnote (m) updated with revised Visit 1 name and timing of completion of questionnaires.

Section 1.3 (Schedule of assessments, Table 2): New footnote (o) added to clarify the samples that are optional for China (not to be collected and analysed until approved by relevant local authorities).

Section 1.3 (Schedule of assessments, Table 2): New footnote (p) added to clarify that AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period is not considered subsequent anticancer therapy.

Section 2.2.6 (Baseline clinico-pathological characteristics): New section added to clarify that disease stage, EGFR mutation type, race, and smoking status may be recorded and monitored during the study.

Section 3 (Objectives and Endpoints, Table 3): Additional exploratory objective and endpoint added 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. Pulmonary function tests removed as a safety endpoint as pre-surgery pulmonary function tests are no longer mandatory.

Section 4.1.1 (Pre-screening and screening period): Text amended to clarify that patients will be given the choice to undergo main screening assessments in parallel to the "central" EGFR mutation. Text also amended to clarify radiological assessments and other clinical data obtained as SoC prior to consent may be used for the study, provided the assessments were obtained within 6 weeks of "randomisation" (amended from "first dose of study drug").

Section 4.1.2 (Neoadjuvant period): Text amended to clarify when a discontinuation visit should be performed, and when the safety follow-up visit will also be performed.

Section 4.1.3 (Surgery period): Text added to clarify the calculation of the corresponding cycles/days for procedures and assessments (independent of dosing delays or interruptions), to note the site must discuss and seek approval from the Study Clinical Lead if surgery cannot be conducted at the site due to unavoidable logistic issues, and to instruct that tumour specimens collected during surgery should be ideally sent to the centralised pathology laboratory within 8 weeks of surgery.

Section 4.1.4 (EFS follow-up period): Text amended to specify that patients must meet adjuvant eligibility criteria (specified in Section 6.1.2.2) prior to starting adjuvant osimertinib. Further amendments to text made to help clarify the timing of visits and evaluations.

Section 4.1.5 (Survival period): Text added to clarify that after recurrence or other EFS event, patients will be followed for overall survival every 3 months until 5 years from surgery (or from date of last neoadjuvant treatment if no surgery is performed) in the last randomised patient.

Section 4.4 (End of study definition): Language relating to the end of study definition was updated to include differences under FDA and EU regulatory requirements.

Section 5.1 (Inclusion criteria): Inclusion criteria 5 amended to include cross-reference to nodal assessment. Inclusion criteria 8 amended to note that creatinine clearance may be assessed by 24-hour urine creatinine.

Section 5.2 (Exclusion criteria): Exclusion criterion 2 guidance text on patients with known HIV infection has been updated to allow for the inclusion of patients with HIV that is well controlled and meets certain criteria. Text added to Exclusion criterion 4 to specify history of another primary malignancy includes any known or suspected synchronous Stage IA primary lung cancer, except if it is planned to be resected during surgery for the Stage II to IIIB N2 lung tumour. Exclusion criterion 10 revised to additionally exclude patients with T4 tumours infiltrating the great vessels, the carina, the trachea, and/or the vertebral body. Exclusion criterion 12 factors that increase the risk of QTc prolongation or arrhythmic events revised into a bulleted list for clarity, and a new note added that results adjusted for hypoalbuminemia are acceptable, if applicable.

Section 5.3.3 (HIV infection): New section added providing guidance on the monitoring of patients with known HIV infection.

Section 6.1.1 (Investigational products; Table 4): Following text removed "(ie, a minimum of 9 weeks total treatment time)" from the Neoadjuvant period for both osimertinib and placebo. Also footnote (b) updated noting patients may also switch from carboplatin to cisplatin at any point during the study.

Section 6.1.1.2.1 (Pemetrexed): Text to added to specify intramuscular injection of Vitamin B12 must be given and that corticosteroid should be given the day prior to, day of, and the day after pemetrexed administration.

Section 6.1.1.2.3 (Carboplatin): Text added to note creatinine clearance may be assessed by 24-hour urine creatinine.

Section 6.1.2.1 (Neoadjuvant period): Text added to note timings are calculated from C1D1 independent of dosing delays and interruptions.

Section 6.1.2.2 (Adjuvant osimertinib during the EFS follow-up period): Section revised to add clarity that the adjuvant period refers to AstraZeneca-supplied osimertinib given in the EFS follow-up period and specify the relevant inclusion and exclusion criteria that need to be met prior to commencing adjuvant treatment. In addition, text added to give timeframes for the commencement of adjuvant osimertinib in the EFS follow-up period relative to surgery (with or without post-operative treatment) or radiotherapy. Text added to the final paragraph of the section to clarify that patients receiving a dose reduction of osimertinib/placebo during neoadjuvant treatment may also be offered osimertinib adjuvant therapy.

Section 6.1.3.1 (Surgery eligibility): Text revised for readability. In addition, instructional text added to discuss the patient with the Study Clinical Lead or delegate if surgery is planned prior to Day 64. In addition, text added to clarify that timing for surgery is counted from C1D1 independent of dosing delays or interruptions, and that a whole-body ^{18}FDG-PET scan includes base of skull to mid-thigh.

Section 6.3.1 (Patient enrolment and randomisation): Prior pulmonary function testing added to the list of assessments that may be used for screening purposes with consent of the patient, if performed within 6 weeks prior to randomisation. Timing of prior screening laboratory procedures and imaging results both amended from 28 days to 6 weeks prior to randomisation.

Section 6.5.1 (Restricted and prohibited concomitant medications): Guidance text added on the monitoring of patients who received prior treatment with immuno-oncology therapies. Table 6 updated to reflect reduction of the time period from 3 months to 3 weeks after the last dose of osimertinib for the use of strong inducers of CYP3A4.

Section 7.1 (Discontinuation of study treatment): Clarified that discontinuation of study treatment is mandatory (not optional) if any treatment discontinuation criteria are met.

Section 8.1.1 (Surgical specimen assessments): Text added to note surgical specimens should ideally be sent within 8 weeks after surgery.

Section 8.1.2.1 (Contrast-enhanced CT scan): Deletion of text "Assessments according to RECIST 1.1 are not collected." Text revised for clarity, additional timepoints added for EFS follow-up beyond 5 years (ie, Week 264 then every 48 weeks [±14 days]), and guidance on the determination of an EFS event. Time period for scans that can be used for baseline changed from within 56 days of first dose to within

6 weeks of randomisation. Definitions added on when pleural effusions can be considered new unequivocal lesions, and clarification on the categorisation of new lesions as local/regional recurrence, distant recurrence, or a new primary malignancy.

Section 8.1.2.2 (Whole-body PET scan): Text added to clarify that a whole-body ^{18}FDG-PET scan includes base of skull to mid-thigh, and to note these scans will assist the exploration of PET-CT radiomic signatures. Clarified that CT scans of diagnostic quality would need to use adequate contrast.

Section 8.1.3 (Overall survival [OS] assessments): Text "primary analysis" clarified to "EFS analysis".

Section 8.3.2 (Clinical safety laboratory assessments; Table 9): Blood creatinine, cystatin C, and blood creatine phosphokinase added to the list of clinical chemistry laboratory assessments to be measured. Text and Table 9 footnote (b) amended to specify that creatinine clearance may be assessed by 24-hour urine creatinine. Additional footnote (e) stating CPK and cystatin C are required in patients after local approval of this CSP amendment.

Section 8.3.5 (Vital signs and body weight): Header amended to include "Body Weight", and text added to note blood pressure and pulse measurements may be assessed sitting if supine is not feasible. Information on body weight measurement was removed from Section 8.3.4 and added to Section 8.3.5 to match Table 1.

Section 8.4.2 (Time period and frequency for collecting AE and SAE information): New table (Table 12) added to outline time period for AE/SAE collection.

Section 8.4.4 (Adverse event data collection): Further information added to clarify that all CTCAE grades should be captured in the eCRF for AEs of ILD/pneumonitis.

Section 8.4.7 (Adverse events based on examinations and tests): Dose modification, interruption, delay of surgery, and/or considered to be clinically relevant by the investigator were added as reasons for a deterioration in protocol-mandated laboratory values, vital signs, ECGs, or ECHO/MUGA scans to be reported as an AE.

Section 8.5.4 (Medication error, drug abuse and drug misuse): Entire section updated with new language, primarily to include additional text relating to drug abuse and drug misuse.

Section 8.5.5 (Reporting of overdose): New section added on reporting of overdose.

Section 8.5.6.2 (Dose adjustment information for osimertinib; Table 14): Dose modification instructions clarified for adverse reactions of ILD/pneumonitis during the neoadjuvant and EFS follow-up periods, and QTc interval >500 msec.

Section 8.5.6.4.1 (ILD/Pneumonitis-like toxicity; Table 17): Further instructional text added to clarify the dosing modification and toxicity management guideline for ILD/pneumonitis events identified during the neoadjuvant period, and EFS follow-up period in subjects receiving adjuvant osimertinib, including the option for investigators to continue or reinitiate adjuvant osimertinib after Grade 1 or 2 ILD/pneumonitis per the toxicity management guidelines in Table 17.

Section 8.5.6.4.4 (Erythema multiforme and Stevens-Johnson syndrome): Guidance added on the new ADR of erythema multiforme and Stevens-Johnson syndrome.

Section 8.5.6.4.5 (Aplastic anaemia): Guidance added on new ADR of aplastic anaemia.

Section 8.5.6.4.7 (Haematological parameters): Toxicity resolution in first paragraph changed to ≤CTCAE Grade 2.

Section 8.6.1 (Pharmacokinetics): Text revised for clarity on timings of sample collections. Also, text added to specify that only osimertinib dosed patients will be analysed in the bioanalytical lab using a validated bioanalytical method. The unblinding to identify the samples will only be available to the bioanalytical lab and this information along with the concentration data will not be shared with any other study personnel until after database lock.

Section 8.6.1.2 (Storage and destruction of pharmacokinetic samples): Specific text referencing the process for sample collection and shipping in China as per the Laboratory Manual is removed.

Section 8.6.3 (Surgical specimen collection): Text added to note surgical specimens to be submitted to the central pathology laboratory ideally within 8 weeks after surgery.

Section 8.7 (Human biological samples: Biomarkers), Section 8.7.1 (Collection of mandatory samples for biomarker analysis; Table 18), Section 8.7.1.2 (Collection of other mandatory samples for exploratory

biomarker analysis), Section 8.7.1.2.1 (Tumour markers), Section 8.7.2 (Collection of optional biomarker samples, Table 19): Text revised in line with the China requirements on biological samples.

Section 8.7.1 (Collection of mandatory samples for biomarker analysis, Table 18): Footnote (d) added to clarify timing of collection of plasma sample for MRD/ctDNA analysis. Footnote (e) added to clarify that it is the specimen tissue for exploratory biomarker and NGS testing that is optional in China.

Section 9.2 (Sample size determination): Text added to clarify the population to be included in the interim analysis of MPR.

Section 9.3 (Populations for analyses): Definition for the resected analysis set clarified; includes all patients who underwent and completed definitive surgical resection.

Section 9.4 (Statistical analyses): Text added to note efficacy analyses to be performed on FAS population, with the exception of DFS analysis which will use the resected analysis set, and safety analysis set to be used for safety and tolerability tables, figures, and listings, unless stated otherwise.

Section 9.4.1.1 (Primary endpoint: Major Pathological Response): Method used for MPR determination added.

Section 9.4.1.2 (Secondary endpoint: Pathological Complete Response): Method for pCR determination added.

Section 9.4.1.3 (Secondary endpoint: Event-free survival): Text revised to clarify the EFS as a key secondary endpoint and the identification of a EFS event in patients who do not undergo surgery or who do not complete definitive surgery for reasons other than progression.

Section 9.5 (Interim analyses): Language revised to be consistent with change made in Section 9.2.

Appendix A 1 (Regulatory and ethical considerations): Text added to state it is the investigator's responsibility to oversee the conduct of the study at the site and to adhere to the specified regulations and guidelines. Under Regulatory Reporting Requirements for SAEs, text added to make reference to adhere to specific regulations. Text also added on regulatory reporting requirements for serious breaches.

Appendix A 6 (Dissemination of clinical study data): Text added regarding timing of submission of technical and lay summaries to EU CTIS.

Appendix A 7 (Data quality assurance): Text added regarding medical oversight of the study and reference to the medical oversight plan. Text altered to reflect the minimum required period for retention of study records and documents.

Appendix B 4 (Medication Error, Drug Abuse and Drug Misuse): Entire section updated with new language primarily to include additional text relating to drug abuse and drug misuse.

Appendix E (Definition of women of childbearing potential and highly effective contraceptive methods): Text changed from "reliable" to "highly effective" contraceptive methods throughout in line with guidance on contraception.

Appendix G (Guidance regarding potential interactions with concomitant medications): Text updated for clarity. Contraindicated drugs phenobarbitone and phenobarbital are the same compound and were combined together into one category to ensure clear guidance on the washout period.

Appendix H (Calculated creatine clearance): Instruction on calculation of creatinine clearance from 24-hour urine collection added.

Throughout document for clarity "adjuvant follow-up period" was changed to "EFS follow-up period" (including an updated study design diagram; see Figure 1), and "MPR (missing)" was changed to "MPR (not evaluable)" in case of residual disease (R1/R2). In addition, typographical errors were corrected and other minor editorial changes were made throughout the document.

CSP Version 2.0: 21 August 2020 Changes to the protocol are summarised below:

The key revision to the CSP v2.0 was to allow patients to receive osimertinib (to be regarded as an investigational product) in the adjuvant study period (at the discretion of the Investigator) which will be supplied by AstraZeneca for a maximum 3-year treatment period.

The above and other additional changes are described in detail below:

- The Table of Contents was updated.
- Synopsis (Rationale) and Section 2.1: The percentage for probability of survival was updated.
- Synopsis (Intervention Groups and Duration): Text updated to reflect that patients may receive adjuvant therapy at the discretion of the Investigator (following discussion with the MDT), including osimertinib, which will be offered (for up to 3 years) to all patients who have completed surgery (+/- chemotherapy post-surgery).
- Synopsis (Statistical methodology): text describing a subgroup analysis comparing event free survival (EFS) in patients with an MPR response with EFS in patients without an MPR response was deleted. The subgroup analysis to compare EFS in patients with an MPR response with EFS in patients without an MPR response was deleted.
- Section 1.2 (Schema): footnote inserted.
- Section 1.3, (Schedule of assessments, Table 1): A footnote (m) was inserted to clarify the timing of pregnancy tests for women of childbearing potential.
- Section 1.3 (Schedule of assessments, Table 1): A footnote (a) was inserted to indicate that upon completion all pre-screening assessments should be entered on the case report form. Footnote l was amended to reflect timing of pregnancy testing. Footnote n was amended to reflect that pathologic mediastinal lymph node evaluation could be performed either histologically or cytologically
- Section 1.3 (Schedule of assessments, , Table 1): Footnote H was amended to clarify the timing for contrast enhanced CT scans. A cross-reference to the Section 8.1.2.1 was added.
- Section 1.3 (Schedule of assessments): Table 2 describing the adjuvant and survival periods was added and text updated to indicate that the second adjuvant visit was scheduled at 12 weeks post-surgery.
- Section 1.3, Schedule of assessments): Table 2 (Footnote a): Text added to clarify that the inclusion and exclusion criteria relevant to initiation of adjuvant therapy must be met prior to commencing treatment
- Section 1.3 (Schedule of assessments), Sections 4.1.1 (pre-screening and screening period) and 8.3.8(Brain MRI/CT): Text was amended to clarify language regarding CT scans without contrast.
- Section 2.2.3.1 (EGFR TKI treatments in early-stage NSCLC): Text regarding study CTONG1104 was deleted.
- Section 2.2.4.1 (Osimertinib in early-stage NSCLC**):** Text relating to the ADAURA study data was deleted.
- Section 2.3.2.2 (Osimertinib in combination with chemotherapy): Text updated regarding safety signals.
- Section 4.1.2: (Adjuvant period); Text amended to clarify that patients assigned to the osimertinib monotherapy arm may receive chemotherapy.
- Section 4.1.4 (Adjuvant period): Text was added to specify that physicians are required to follow the most recent NCCN, ESMO, Pan-Asia adapted ESMO or other internationally recognised guidelines while planning adjuvant treatment and that at the treating Investigator's discretion, osimertinib would be made available to patients by AstraZeneca for a maximum 3-year treatment period, or until disease recurrence. Text was updated to indicate that the second adjuvant visit was scheduled at 12 weeks post-surgery.
- Section 5.1 (Inclusion criteria): Inclusion criterion 5 was updated to reflect that patients with non-squamous NSCLC are eligible for the study.
- Section 5.1 (Inclusion criteria): Inclusion criterion 8 was amended to correct the required creatinine clearance value for study eligibility.
- Section 5.1 (Inclusion criteria); Inclusion criterion 9 was updated to reflect that patients must have a life expectancy of > 6 months prior to randomisation.
- Section 5.2 (Exclusion criteria): Exclusion criterion 12 was amended to provide flexibility regarding the method by which mean resting corrected QT interval is calculated (machine-derived or manual).
- Section 5.2 (Exclusion criteria): Exclusion criterion was inserted (exclusion criterion 25) to align with the COVID-19 requirements regarding the patient’s ability to understand/comply with the study procedures, restrictions and requirements.

- Section 5.3.1 (Pregnancy); Text added to clarify the potential for a reduced exposure to hormonal contraception during the study and the requirement to use an acceptable form of contraception for at least 6 months after discontinuing platinum-based chemotherapy.
- Section 5.4 (Screen failures): Text was added to clarify that patients who do not meet the criteria for participation in the study (ie, screen failures) may be rescreened once.
- Section 6.1.1 (Investigational products): Text was updated to reflect that if osimertinib was prescribed in the adjuvant phase AstraZeneca would supply treatment for a maximum 3-year period and that in this scenario, osimertinib would continue to be regarded as a study treatment.
- Section 6.1.1 (Table 4): Dosing instructions for osimertinib in the adjuvant period were added.
- Section 6.1.1.1 (Osimertinib [AZD9291] or matching placebo dosing); The timing for dispensing osimertinib was clarified. Details regarding the packaging were updated.
- Section 6.1.2.1 and 6.1.2.2: Sections describing the neoadjuvant and adjuvant periods were created. Text providing the restrictions for osimertinib adjuvant dosing was added.
- Section 6.1.1.2.3: AUC units amended from mg/ml/min to mg/mL·min. Additional text to clarify that in the Calvert Formula used for determining the dose of carboplatin, GFR is estimated by calculated creatinine clearance using the Cockcroft-Gault Equation.
- Section 6.1.3.1 (Surgical eligibility): Criterion 7 was amended to align the timepoint for the DLCO predicted postoperative value with the ESMO guidelines. Language was added to permit flexibility in the experience of the surgeon permitted to perform the pulmonary resection.
- Section 6.1.3.2 (Preoperative mediastinal lymph node staging): Text regarding tumour features which should be considered for pathologic mediastinal evaluation and preoperative mediastinal lymph node staging was added.
- Section 6.1.3.5 (Nodal assessment):Text clarifying the nodal assessments for patients considered for pathologic mediastinal lymph node evaluation was added.
- Section 6.5 (Concomitant therapy): Text clarifying that for patients treated with IP-osimertinib in the adjuvant phase, the collection of concomitant medications should continue per Table 2.
- Section 6.5.1 (Restricted and prohibited concomitant medications): Text updated to prohibit the concomitant use of live vaccines and to restrict the use of nephrotoxic and ototoxic therapies.
- Section 7.1 (Discontinuation of study treatment): duplicate discontinuation criteria was deleted.
- Section 7.1.1 (Procedures for premature discontinuation of study treatment): Text updated to reflect that a discontinuation visit should be performed for patients receiving AstraZeneca-supplied osimertinib in the adjuvant period of the study.
- Section 7.1.1.1 (Follow-up of patients' post-premature discontinuation of study treatment); Text added to state that a safety follow-up visit at 28-days (+14 days) after the last dose of osimertinib should be performed for patients receiving AstraZeneca-supplied osimertinib in the adjuvant period of the study.
- Section 8.1.1 (Surgical specimen assessments): Text updated to clarify the surgical specimen assessment process.
- Section 8.1.2 (Pathologic mediastinal lymph node assessments at screening): Section deleted.
- Section 8.3.1 Text added to describe testing for Covid-19.
- Section 8.3.6 (Electrocardiograms): text updated to reflect that for patients receiving AstraZeneca-supplied osimertinib in the adjuvant period of the study, ECGs should be performed if clinically indicated.
- Section 8.3.7 (Echocardiogram/MUGA scan): Text was updated to specify that an echocardiogram or MUGA scan will be performed during the screening period, during the pre-surgical assessment, as clinically indicated (neoadjuvant phase) and every 12 weeks for 24 weeks (patients receiving osimertinib in the adjuvant phase).
- Section 8.4.2 (Time period and frequency for collecting AE and SAE information): Text added to specify timing of SAE and AESI collection for patients in the adjuvant phase who are receiving osimertinib treatment only.

- Section 8.5.5.1 (General dose adjustments for adverse events): Text provided to clarify principles of dose modification of chemotherapy and osimertinib/placebo. Additional text added requiring patients who discontinue all treatment because of toxicity to be followed until resolution of the toxicity.
- Section 8.5.5.2 (Dose adjustment information for osimertinib): clarification regarding osimertinib toxicity management.
- Section 8.7.1.2 (Collection of other mandatory samples for exploratory biomarker analysis): Text was updated to clarify the tumour tissues that will be collected for biomarker analysis.
- Section 9.4 (Statistical analysis): text updated to reflect that summaries of data relating to patients diagnosed with COVID-19 and the impact of COVID-19 on the study may be generated.
- Section 9.4.1.3 (Secondary endpoint: Event free survival): Text updated regarding the length of follow-up after the last patient was randomised and the timing of the final analysis of EFS.
- Section 9.4.1.4 (Secondary endpoint: Overall survival): Text was updated to clarify the length of time patients will be followed up for OS after randomisation.
- Section 9.4.1.6 (Secondary endpoint: Downstaging): Text was updated to clarify that downstaging will be formally assessed for patients with pathological staging available at both timepoints (N2 patients becoming N1/N0 or N1 to N0 at the time of surgery).
- Section 9.4.5 (Methods for multiplicity control): Text updated to clarify that the analysis of EFS will use the Haybittle-Peto boundary for interim and final analysis to control the overall 5% type I error rate such that the analysis is time driven rather than event driven and that the EFS final analysis will occur 3 years after the last subject finishes surgery.
- Section 9.5 (Interim analyses): Text was updated to reflect the interim analysis and that the final analysis of EFS would be conducted when all patients had had the opportunity for at least 3 years follow-up post-surgery
- Appendix H was updated to correct an error in units in the formula for calculated creatinine clearance and to amend the lettering of footnotes.
- Typographical errors were corrected throughout the document.

CSP Version 1.0: 10 March 2020
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Synopsis

International co-ordinating Investigator:

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Protocol title:

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)

Rationale:

While the primary treatment for early-stage resectable non-small cell lung cancer (NSCLC) (Stages I to III) is curative surgery, the prognosis for patients treated with surgery alone remains poor. Patients with pathologic stage IIA NSCLC have 65% probability of survival at 60 months, which is reduced to 41% for stage IIIA NSCLC (8th edition staging) (Goldstraw et al 2016).

In this treatment setting, there are numerous factors that make neoadjuvant therapy advantageous: earlier treatment of micrometastatic disease, reduction in tumour burden, evaluation of tumour sensitivity in vivo, prevention of tumour seeding at the time of surgery, and possible improved compliance with therapy (Farray et al 2005, Felip et al 2010).

According to National Comprehensive Cancer Network (NCCN) guidelines chemotherapy is the only recommended neoadjuvant treatment for stage II- III NSCLC patients (regardless of epidermal growth factor receptor [EGFR] mutation status), and whilst a number of studies have demonstrated encouraging results relating to the clinical benefit of neoadjuvant chemotherapy in early-stage NSCLC (eg, improvements in progression-free survival [PFS] and overall survival [OS]) (Pisters et al 2010, Scagliotti et al 2012, Song et al 2010, NSCLC Meta-analysis Collaborative Group 2014), further improvement is still needed.

Consequently, whilst there are currently no approved EGFR-tyrosine kinase inhibitor [TKI] therapies for use in the neoadjuvant treatment setting in EGFR mutation-positive (EGFRm)

patients, recent evidence has been obtained that indicates that EGFR-TKI treatments (eg, gefitinib, erlotinib or afatinib) when given in the neoadjuvant setting can achieve clinically meaningful results in EGFRm NSCLC patients, in terms of both tumour response (pathological response and objective response) and survival (Zhong et al 2018a, Xiong et al 2018, Zhong et al 2015, Sequist et al 2018, Zhong et al 2018b). Furthermore, the osimertinib adjuvant Phase III ADAURA trial was unblinded early following a recommendation from the IDMC based on its determination of overwhelming efficacy, compared to placebo. This was the first targeted agent in a global trial to show statistically significant and clinically meaningful improvement of DFS in adjuvant treatment of NSCLC patients following surgery (Herbst et al 2020). Given these positive osimertinib data in the adjuvant setting, and the preliminary data obtained in EGFR-TKI targeted therapies in the early disease setting, in addition to the compelling data in favour of osimertinib in the advanced treatment setting when compared with standard-of-care (SoC) chemotherapy (AURA3 study; Mok et al 2017) and against SoC EGFR-TKI treatments (erlotinib and gefitinib) in the first-line setting (FLAURA study; Soria et al 2018, Ramalingam et al 2019), there is a strong rationale to suggest that osimertinib may provide clinical benefit in the neoadjuvant treatment setting for EGFRm patients.

Objectives and Endpoints:

Primary objective:	**Endpoint/variable:**
To determine the efficacy of osimertinib as monotherapy or in combination with chemotherapy compared to chemotherapy alone, as neoadjuvant treatment	• Major pathological response (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), event-free survival (EFS), disease free survival (DFS), downstaging and Overall survival (OS).	• pCR (defined as absence of any residual cancer cell in the surgical specimen post-surgery, as assessed per central pathology laboratory) • N2 to N0/N1and 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 objective:	**Endpoints/variables:**
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 event 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 IP-related AEs

Overall design:

This is a Phase III, randomised, controlled, multi-centre, 3-arm study of neoadjuvant osimertinib as monotherapy or in combination with chemotherapy, versus SoC chemotherapy alone, for the treatment of patients with EGFRm (Ex19del and/or L858R), resectable NSCLC.

Number of Participants:

Approximately 351 patients with histologically or cytologically documented EGFRm (Ex19del and/or L858R) NSCLC with resectable (clinical stage II to IIIB) disease will be randomized 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 mainland China], and Chinese living in mainland China), and mutation type (Ex19del versus L858R).

Sample size estimates have been calculated using EAST® version 6.4.

Intervention Groups and Duration:

The randomised treatment regimens are as follows:

- 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 1)

  or

- Osimertinib 80 mg QD + investigator's choice of chemotherapy (as above) (Arm 2)

  or

- Osimertinib 80 mg QD as monotherapy (Arm 3)

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

Patients assigned to a chemotherapy-containing arm (Arm 1 or Arm 2) will receive 3 cycles of chemotherapy (1 cycle = 21 days), 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. Osimertinib/placebo may be continued up to the date of surgery in all treatment arms, at the discretion of the Investigator. Surgery is to be performed as soon as possible after the end of the 9-week neoadjuvant treatment period, up to a maximum of 12-weeks (+7 days with Sponsor approval) following the start of neoadjuvant study treatment.

All patients who underwent surgery, or who did not have surgery for any reason other than disease progression, will subsequently enter the EFS follow-up period. Patients may receive adjuvant therapy at the discretion of the Investigator (following discussion with the MDT), including osimertinib, which will be offered (for up to 3 years) to all patients who have completed surgery (+/- chemotherapy post-surgery and +/- post-operative radiotherapy). All patients in the EFS follow-up period are to be evaluated at 12 weeks post-surgery, at 24 weeks post-surgery, and subsequently every 24 weeks until Week 264 (5-years) then every 48 weeks (±14 days) until disease recurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first).

Data Monitoring Committee:

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

Statistical methodology:

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. "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.

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.

Per primary analysis, MPR will be calculated as number of patients with MPR response in the full analysis set (FAS) (ie, all randomised patients). The analysis of MPR will be performed using a Cochran-Mantel-Haenszel (CMH) test, stratified by disease stage (Stage II versus Stage III), race (Non-Asian, Other Asian [excluding Chinese living in mainland China] and Chinese living in mainland China), and mutation type (Ex19del versus L858R). The treatment effect will be estimated by the odds ratio together with its corresponding 100 * (1-alpha)% confidence interval (CI) and p-value. The FAS population will be used.

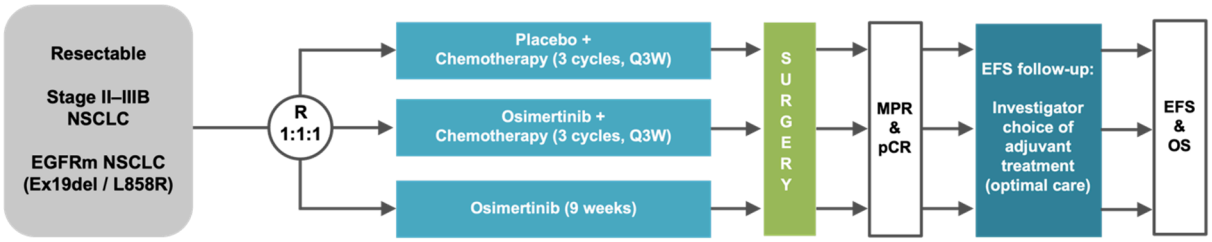
Subgroup analyses will be conducted by comparing MPR between the experimental arm (either Arm 2 or Arm 3) and the control (Arm 1) in 3 stratification factors: disease stage, race, and mutation type.

Details of the analysis of the secondary efficacy endpoints (pathological complete response [pCR], EFS, disease free survival [DFS] and overall survival [OS]) can be found in Section 9 of the main Clinical Study Protocol. 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 at the MPR primary analysis (0.002% alpha has been spent in MPR interim analysis).

1.2 Schema

The general study design is summarized in Figure 1.

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 (for up to 3 years) to all patients who have completed surgery (+/- chemotherapy post-surgery and +/- post-operative radiotherapy).

1.3 Schedule of activities (SoA)

The procedures for the screening, neoadjuvant, and surgical periods of this study are presented in Table 1. The procedures for the EFS follow-up and survival periods are presented in Table 2.

Table 1 Schedule of assessments (Screening, Neoadjuvant, and Surgical periods)

Study Period	Screening (see Section 4.1.1)			Neoadjuvant (see Section 4.1.2)				Surgery (see Section 4.1.3)			Safety follow-up [e]	For details, see Section
Visit	Pre-screening [a]	Screening	Treatment Allocation [b]	C1	C2	C3	Treatment discont-inuation (+3 days) [c]	Pre-surgical assessment	C4 (osi / placebo) [d]	Surgery		
Timepoint (window [days])	NA	D-28 to -1	D-7 to -1	D1	D22 [cc] (-2 to +3 days)	D43 [cc] (-2 to +3 days)		D64 (-1 to +21 days)	D64 (+3 days)	D64 to D84 (+7 days) [f]	28 days after last dose of either IP or surgery (+14 days)	
Informed consent [g]												
Informed consent for pre-screening *(if applicable)*	X											4.1.1
Informed consent for study participation		X [g]										5.1
Informed consent for Genomics Initiative sample (whole blood) *(optional)*		X										5.1
Study procedures												
Eligibility criteria	X	X										5.1 & 5.2
Demography, including baseline characteristics and tobacco use	X	X										6.3.1
Surgery eligibility criteria								X [h]				6.1.3.1
Physical examination		X					X	X	X			8.3.4
Vital signs, body weight		X		X	X	X	X	X	X			8.3.5
Covid-19 test [i]	←			ACI (see Footnote i for details)							→	8.3.1
ECG [j]		X		ACI				X			ACI	8.3.6
ECHO/MUGA (for LVEF)		X [g]						X			ACI	8.3.7
Pulmonary function testing		X [g]						ACI				6.1.3.3
Concomitant medications	←			See Footnote k for a description of the data collection period						→	X	6.5
Subsequent anticancer therapy							X				X	8.1.3
Laboratory assessments												
Clinical chemistry [l]		X		X	X	X	X	X	X		ACI	8.3.2

Study Period	Screening (see Section 4.1.1)			Neoadjuvant (see Section 4.1.2)				Surgery (see Section 4.1.3)			Safety follow-up [e]	For details, see Section
Visit	Pre-screening [a]	Screening	Treatment Allocation [b]	C1	C2	C3	Treatment discont-inuation (+3 days) [c]	Pre-surgical assessment	C4 (osi / placebo) [d]	Surgery		
Timepoint (window [days])	NA	D-28 to -1	D-7 to -1	D1	D22 [cc] (-2 to +3 days)	D43 [cc] (-2 to +3 days)		D64 (-1 to +21 days)	D64 (+3 days)	D64 to D84 (+7 days) [f]	28 days after last dose of either IP or surgery (+14 days)	
Haematology [l]		X		X	X	X	X	X	X		ACI	8.3.2
Urinalysis		X		ACI								8.3.2
Pregnancy test [m]		X		X	X	X			X			8.3.3
HIV testing [ee]		X [ee]	← See Footnote ee for a description of the data collection period →									5.3.3
Efficacy evaluation												
Whole-body ^{18}FDG-PET scan		X [g]						X				8.1.2.2
Contrast-enhanced CT scan [n]		X [g]						X				8.1.2
Pathological evaluation [o]		X								X		6.1.3.5
Brain MRI (preferred) or CT		X [g]										8.3.9
Surgical specimen for pathological assessment										X [p]		8.1.1
Monitoring												
ECOG performance status		X		X	X	X	X	X	X		X	8.3.8
AE/SAE assessment [q]	← See Footnote k for a description of the data collection period →											8.4
Pre-chemotherapy treatment medication [r]												
Folic acid [s]			X	X	X	X						6.1.1.2.1
Vitamin B12 [t]			X									6.1.1.2.1
Corticosteroid [u]			X	X	X	X						6.1.1.2.1
IP administration												
Treatment allocation			X									6.3.1
Osimertinib / Placebo *(if applicable)*				X	X	X [v]			X [v]			6.1.1.1
Chemotherapy *(if applicable)*				X	X	X						6.1.1.2

Study Period	Screening (see Section 4.1.1)			Neoadjuvant (see Section 4.1.2)				Surgery (see Section 4.1.3)			Safety follow-up [e]	For details, see Section
Visit	Pre-screening [a]	Screening	Treatment Allocation [b]	C1	C2	C3	Treatment discont-inuation (+3 days) [c]	Pre-surgical assessment	C4 (osi / placebo) [d]	Surgery		
Timepoint (window [days])	NA	D-28 to -1	D-7 to -1	D1	D22 [cc] (-2 to +3 days)	D43 [cc] (-2 to +3 days)		D64 (-1 to +21 days)	D64 (+3 days)	D64 to D84 (+7 days) [f]	28 days after last dose of either IP or surgery (+14 days)	
Patient Reported Outcome, health economics, and other study questionnaires												
EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L [w]				X	X	X	X	X				8.2
TransCelerate study participant feedback questionnaire *(optional)*				X		X						8.10
HOSPAD [x]				X	X	X	X	X				8.9
Biomarker analysis												
Tumour FFPE sample for central EGFR mutation analysis *(mandatory where available)* [y]	X	X										8.7.1.1
Plasma sample for central EGFR mutation testing *(mandatory)*	X [dd]	X [dd]										8.7.1.1
Blood sample for CHIP & HLA analysis *(mandatory)* [z]				X								8.7.1.2
Surgical specimen tissue for exploratory biomarker and NGS testing *(mandatory)* [z]										X		8.7.1.2
Plasma sample for MRD/ctDNA analysis *(mandatory)* [z]				X				X				8.7.1.2 & 8.7.2
Pharmacokinetic measurements												
Pre-dose blood sample [aa]					X	X						8.6.1
Post-dose blood sample [aa]					X	X						8.6.1

Study Period	Screening (see Section 4.1.1)			Neoadjuvant (see Section 4.1.2)				Surgery (see Section 4.1.3)			Safety follow-up [e]	For details, see Section
Visit	Pre-screening [a]	Screening	Treatment Allocation [b]	C1	C2	C3	Treatment discont-inuation (+3 days) [c]	Pre-surgical assessment	C4 (osi / placebo) [d]	Surgery		
Timepoint (window [days])	NA	D-28 to -1	D-7 to -1	D1	D22 [cc] (-2 to +3 days)	D43 [cc] (-2 to +3 days)		D64 (-1 to +21 days)	D64 (+3 days)	D64 to D84 (+7 days) [f]	28 days after last dose of either IP or surgery (+14 days)	
Genomics Initiative *(optional)*												
Genomics blood sample *(optional)* [bb]				X								8.8

Abbreviations: ACI, As clinically indicated; AE, Adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; C, Cycle; CHIP, Clonal haematopoiesis of indeterminate potential; CT, Computed tomography; ctDNA, Circulating tumour DNA; D, Day; DNA, Deoxyribonucleic acid; EBUS, endobronchial ultrasound; ECG, Electrocardiogram; ECHO, Echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, Electronic Case Report Form; EGFR, Epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; ePRO, Electronic PRO; EQ-5D-5L, EuroQoL 5-Dimension, 5 Level health state utility index; EUS, oesophageal ultrasonography; FDG-PET, Fluorodeoxyglucose positron emission tomography; FFPE, Formalin fixed and paraffin embedded; FNA, Fine needle aspirate; HIV, Human immunodeficiency virus, HLA, Human leukocyte antigen; HOSPAD, Hospital resource use module; ICF, Informed consent from; IFU, Instructions for use; IgG, immunoglobulin G; IP, Investigational product; LFT, Liver function test; LVEF, Left ventricular ejection fraction; MRD, minimal residual disease; MRI, Magnetic resonance imaging; MUGA, Multi-gated acquisition (scan); NA, Not applicable; NGS, Next-generation sequencing; PET, Positron emission tomography; PK, Pharmacokinetic; PRO, Patient-reported outcome; Q3W, Every 3 weeks; QLQ C30, 30-item Core Quality of Life Questionnaire; QLQ-LC13, 13-item Lung Cancer Quality of Life Questionnaire; SAE, Serious adverse event; TKI, Tyrosine kinase inhibitor.

Each neoadjuvant treatment cycle is 21 days (3 weeks) in duration, unless dosing needs to be held for toxicity reasons. All assessments occurring on study visit days are to be performed prior to receiving study treatment, unless otherwise indicated.

a. Upon completion, all pre-screening activities should be entered in the eCRF.

b. Can be conducted by phone. Every effort should be made to minimize the time between randomization and starting treatment.

c. A study treatment discontinuation visit should be performed only for patients who prematurely discontinue 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(s). For patients who complete 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.

d. Required for patients who are to be administered osimertinib/placebo treatment beyond the end of C3 (D64+). Visit will comprise osimertinib/placebo dispensing and safety assessments.

e. Required for all patients 28-days after the final dose of study treatment or surgery (whichever is the latter). At a minimum telephone contact should be made with the patient. If a laboratory or safety assessment was abnormal and clinically significant at treatment discontinuation, a site visit is required.

f. Surgery is expected to be undertaken within 3 weeks from the end of neoadjuvant treatment (from D64 to D84, counted from C1D1 independent of dosing delays or interruptions). In exceptional circumstances (and with prior agreement from the Sponsor study physician) this surgical period may be extended by 1 additional week (ie, must occur on or before D91, counted from C1D1 independent of dosing delays or interruptions).

g. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. To optimise the screening process for patients, consent can be provided either in a 2-step process (pre-screening followed by main consent) or

directly via the main consent form. Main consent may be taken prior to 28-day window, if required. The screening period of 28-days will then start with the first study-related assessment. All patients are asked to provide consent during pre-screening or screening to supply a sample of their tumour (archived or newly acquired tumour FFPE sample) for entry into this study. The collection of additional biopsies upon progression is strongly encouraged. If laboratory or imaging procedures, ECHO/MUGA or pulmonary function testing were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory (except for EGFR testing), imaging results, ECHO/MUGA, and pulmonary function testing must have been obtained within 6 weeks of randomisation (See Section 8.1.2.1). Diffusing capacity of the lungs for carbon monoxide (DLCO) evaluation is recommended during pulmonary function testing, particularly if forced expiratory volume in 1 second (FEV1) is ≤40% predicted.

h. A further eligibility check should also be performed at the pre-surgical assessment visit to ensure patient eligibility for surgery (see Section 6.1.3.1).

i. A Covid-19 test will be performed as clinically indicated/according to local regulations.

j. All mandated ECGs should be performed in triplicate.

k. AEs (including SAEs) **related to study procedures** should be collected from the time of signature on the Prescreening ICF, until screen failure or upon signing the Screening ICF. The collection of all AEs/SAEs and concomitant medications should commence at the signing of the Screening ICF for the study and continue throughout the neoadjuvant period (until 90 days post-surgery for patients undergoing surgery, or 28 days after the last dose of neoadjuvant IP for patients who did not undergo surgery). Data collection may be conducted by phone.

l. Serum or plasma clinical chemistry (including LFT monitoring) and haematology may be performed more frequently if clinically indicated. If screening clinical chemistry, haematology and urinalysis assessments are performed within 14 days prior to C1D1, they do not need to be repeated on C1D1 providing the patient's clinical condition has not changed. Results for full blood count, LFTs, electrolytes, and creatinine must be available before commencing study treatment on D1 of each treatment cycle (within 3 days) and reviewed by the treating physician or Investigator prior to dosing. Creatine phosphokinase (CPK) and cystatin C are required in patients randomised after local approval of CSP v3.

m. **For women of childbearing potential only**. Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be conducted within 14 days of the first dose of study treatment and during study treatment as required by the study physician. Women of childbearing potential are required to have a pregnancy test within 14 days prior to the first dose of study drug and then Q3W prior to IP administration on the first day of each treatment cycle. Pregnancy test may occur on D1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

n. Scan(s) should comprise the chest and abdomen (including adrenal glands and liver).

o. Pathologic mediastinal lymph node evaluation can be performed either histologically or cytologically (via mediastinoscopy, EBUS, EUS, or other technique) is required for any patient with CT-enlarged or PET-positive mediastinal lymph nodes (N2). If pathologic mediastinal lymph node evaluation procedures were performed as part of clinical practice prior to signing consent, these can be used for screening purposes with consent of the patient.

p. The patients' Pathology Report from local laboratory should be submitted together with surgical samples.

q. For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications should be included.

r. For patients randomised to a chemotherapy-containing treatment arm only

s. Folic acid should be administered 5-7 days prior first infusion of pemetrexed and daily during the treatment period. Treatment should continue for 21 days after pemetrexed discontinuation.

t. Vitamin B12 (1000 mcg or 1 mg as an intramuscular injection) must be given and should be administered within 7 days prior to pemetrexed infusion.

u. Corticosteroids should be given 1 day prior to pemetrexed, on the same day as each pemetrexed administration, and 1 day after receiving pemetrexed.

v. At the discretion of the Investigator, the administration of osimertinib/placebo may be continued to the date of surgery. See Section 6.1.1.1 for further details.

w. PRO questionnaires will be administered using a site-based, ePRO device. At C1D1, and following visits, ePRO should be completed prior to any other assessments and prior to dosing. PRO questionnaires do not need to be completed at any visit conducted via telephone. In case of dose delays and/or unscheduled PRO assessments, every attempt should be made to resume subsequent PRO assessments according to the original PRO visit schedule.

x. At each visit, sites are to review if a hospital admission has been made since the last visit; if so, then HOSPAD should be completed. This module should be completed whenever the patient has attended or been admitted to the hospital (ie, each hospital admission, outpatient, or emergency room attendance encountered). It excludes routine follow-up clinic visits.

y. This assessment may be performed once, either in the pre-screening period or the 28-day screening period depending on the patient's consenting process (see Footnote g). Patients are eligible to be considered for inclusion in the study if they have tumours that 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, Exon 20 insertions, S768I and L861Q), as detected by the cobas® EGFR Mutation Test v2 in a tumour tissue sample (submitted during either pre-screening or screening) with preserved tumour tissue architecture (eg, core needle biopsy) by prospective testing in central lab. Enrolment based on a pre-existing EGFR-mutation positive tumour test result using either the cobas® EGFR Mutation Test v2 or FoundationOne® CDx is also allowed, and tumour tissue sample should be provided (where available) for retrospective testing using cobas® EGFR Mutation Test v2 in central lab (EGFR mutation status result not needed to proceed with patient randomization in these cases). In the case that neither tumour tissue sample with preserved tumour tissue architecture, nor pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx EGFR test result per IFU from a tumour sample is available, EGFR mutation status can be centrally confirmed, when permitted by AstraZeneca, in a tumour FFPE FNA sample, collected per SoC prior to, or during, screening, using the Idylla™ EGFR Mutation Test. Provision of additional tumour FFPE FNA samples, if available, is requested for future confirmation testing using an FDA approved FNA test. The total number of tumour FFPE FNA slides required can be found in the Laboratory Manual. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment. Any remaining tumour samples and DNA extracts following completion of central EGFR testing may be used for diagnostic development and exploratory biomarker testing, including NGS. See Section 8.7.1.1 for further details.

z. Optional sample in China. Samples will only be collected and analysed in China after approval by relevant local authorities.

aa. Sample collection will occur at pre-dose (within 1 hour before osimertinib/placebo dosing) and 0.5 to 2 hours post-dose at D22 (C2D1) and D43 (C3D1). For chemotherapy-containing treatment arms (Arms 1 and 2), osimertinib PK samples at C2D1 and C3D1 should be collected on the day of the chemotherapy dosing for that cycle. For osimertinib/placebo PK (Arms 1 to 3), sample collection should only be taken if the patient has received 7 days of continuous osimertinib/placebo dosing prior to that specific PK measurement. If the dosing for chemotherapy or osimertinib/placebo is altered due to interruption or modified for any other reason, then the collection of this PK sample should be performed at the next scheduled dosing of chemotherapy and osimertinib.

bb. The sample for Genomics Initiative will be obtained on D1 pre-dose (at or after randomization). If, for any reason, the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetic analysis during the study. Ensure genetic consent has been provided prior to sample collection. Blood samples for Genomics Initiative will not be collected in China as per local regulations.

cc. D22 (corresponding to C2D1) and D43 (corresponding to C3D1) assume no dosing delays or interruptions prior to C3. If there may be dosing delays or interruption, the days should be counted from C1D1.

dd. To be collected at either the pre-screening or screening visit.

ee. Patients should be tested for HIV prior to randomisation if required by local regulations or Institutional Review Board (IRB)/Independent Ethics Committee (IEC). In patients with known HIV infection that is well controlled, the patient's viral RNA load and CD4+ cell count should be monitored per local SoC (eg, every 3 months).

Table 2 Schedule of assessments (EFS Follow-up and Survival Periods)

STUDY PERIOD	EFS FOLLOW-UP [b] (see Section 4.1.4)				SURVIVAL (see Section 4.1.5)	For details, see Section
Visit			Adjuvant IP-osimertinib treatment discontinuation	Safety follow-up [b]	Survival status [d]	
Timepoint (window [days])	Adjuvant IP-osimertinib treatment decision visit [b]	Wk 12, Wk 24, then Q24W until Wk 264 (±14 days), then Q48W (±14 days) thereafter [b]	Within 3 days after last dose of osimertinib or decision to discontinue osimertinib [c]	28 days after last dose of IP-osimertinib (+14 days)	Every 3-months (±14 days)	
Osimertinib IP dispensing / administration ***(as applicable, per Investigator choice)***						
Eligibility Criteria [a]	X					6.1.2.2
Osimertinib IP dispensing [e]	X	X				6.1.1.1 & 6.1.2.2
SAE/AESI assessment [f]	X	X	X	X		8.4.1
Concomitant medications [f]	X	X	X	X		6.5
Covid-19 test [g]	←	ACI (see Footnote g for details)		→		8.3.1
Pregnancy test [h]	X	X				8.3.3
Haematology / Clinical chemistry [i]	ACI	ACI	X	ACI		8.3.2
ECHO/MUGA (for LVEF) [j]	X	X (Wk 12 and Wk 24 only)		ACI		8.3.7
ECG	ACI	ACI		ACI		8.3.6
Study procedures						
Physical examination	X	X				8.3.4
Subsequent anticancer therapy [p]	X	X	X	X	X	8.1.3
HIV testing [q]	←	See Footnote q for a description of the data collection period		→		5.3.3
Efficacy evaluation						
Contrast-enhanced CT scan [k]		X [l]				8.1.2
Brain MRI (preferred) or CT		X [u] (at recurrence only)				8.3.9
Patient Reported Outcome, health economics, and other study questionnaires						
EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L [m]	X	X				8.2
TransCelerate study participant feedback questionnaire *(optional)*		X (Wk 24 only)				8.10

STUDY PERIOD	EFS FOLLOW-UP [b] (see Section 4.1.4)				SURVIVAL (see Section 4.1.5)	For details, see Section
Visit			Adjuvant IP-osimertinib treatment discontinuation	Safety follow-up [b]	Survival status [d]	
Timepoint (window [days])	Adjuvant IP-osimertinib treatment decision visit [b]	Wk 12, Wk 24, then Q24W until Wk 264 (±14 days), then Q48W (±14 days) thereafter [b]	Within 3 days after last dose of osimertinib or decision to discontinue osimertinib [c]	28 days after last dose of IP-osimertinib (+14 days)	Every 3-months (±14 days)	
HOSPAD [n]	X	X				8.9
Biomarker analysis						
Plasma sample for MRD/ctDNA analysis *(mandatory)* [o]	X [t]	X				8.7.1.2 & 8.7.2
Additional tumour FFPE tissue for exploratory research *(optional)* [r]		X [b, s] (at recurrence only)				8.7.2
Survival follow-up						
Survival status					X	4.1.5

Abbreviations: ACI, As clinically indicated; AESI, Adverse event of special interest; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CT, Computed tomography; ctDNA, Circulating tumour DNA; DNA, Deoxyribonucleic acid; ECG, Electrocardiogram; ECHO, Echocardiogram; EFS, Event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL 5-Dimension, 5 Level health state utility index; FFPE, Formalin-fixed paraffin-embedded; HOSPAD, Hospital resource use module; IP, Investigational product; LVEF, Left ventricular ejection fraction; MRD, minimal residual disease; MUGA, Multi-gated acquisition (scan); QLQ C30, 30-item Core Quality of Life Questionnaire; QLQ-LC13, 13-item Lung Cancer Quality of Life Questionnaire; QXW, Every X weeks; SAE, Serious adverse event; Wk, Week.

a. Please refer to Section 6.1.2.2 for AstraZeneca-supplied adjuvant osimertinib eligibility criteria.

b. In the EFS follow-up period, all patients who underwent and completed surgery will be followed up at 12 weeks post-surgery, 24 weeks post-surgery, and subsequently every 24 weeks until Week 264 (5-years), then every 48 weeks thereafter or until approximately 5.5 years after the last patient is randomised. In addition, all patients who underwent and completed surgery will have an Adjuvant IP-osimertinib treatment decision visit where the investigator will decide whether the patient is eligible for and will commence adjuvant IP osimertinib; this visit may be scheduled at the investigator's discretion but must be prior to 12 weeks post-surgery if no post-operative treatment is given or prior to 26 weeks post -surgery if adjuvant chemotherapy is given. If feasible, the Adjuvant IP-osimertinib treatment decision visit may be combined with the Safety Follow-Up visit after surgery or last neoadjuvant treatment (in Table 1) or the visit at 12 weeks post-surgery or 24 weeks post-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 visit will be conducted 12 weeks from the date of last neoadjuvant treatment, then 24 weeks from the date of last neoadjuvant treatment, and subsequently every 24 weeks until Week 264 (5 years), then every 48 weeks thereafter. Patients who experience disease recurrence during the EFS follow-up period will enter the survival period (see Section 4.1.4). Recurrence detected outside of a scheduled visit must be entered as an unscheduled visit. If possible, an optional tumour FFPE tissue sample for exploratory analysis (to better understand potential mechanisms of resistance to therapies via exploratory biomarker work including but not limited to NGS testing), and a plasma sample (to aid ctDNA testing) should be collected at this unscheduled disease progression visit (see Section 8.7.2).

c. **Only applicable to patients receiving AstraZeneca-supplied adjuvant osimertinib as an IP in the EFS follow-up period**. A treatment discontinuation visit and 28-day Safety follow-up visit will be performed upon discontinuation of osimertinib for any reason (see Section 7.1.1). If the decision to discontinue osimertinib is made 28 days after

last dose or later, the treatment discontinuation visit may be combined with the Safety follow-up visit. Patients without recurrence will then continue to have EFS follow-up visits according to the schedule in Table 2 to assess disease recurrence until the end of the study.

d. Patients who fail to undergo or complete surgery due to disease progression, or who experience disease recurrence at any time during the study will enter the survival period. These patients will continue to be followed up for survival status every 3 months until death, withdrawal of consent, or the final OS analysis at 5 years (see Section 4.1.5).

e. Patients may be administered osimertinib treatment (to be supplied by AstraZeneca every 12 weeks for a maximum of 3-years) in the EFS follow-up period at the discretion of the treating Investigator.

f. **Only applicable to patients receiving AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period**: SAEs and AESIs (see Section 8.4.12), and concomitant medications should be collected at every visit, including IP dispensing visits whilst patients remain on treatment.

g. A Covid-19 test will be performed as clinically indicated/according to local regulations.

h. **Only applicable to women of childbearing potential receiving AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period**: Women of childbearing potential are required to have a pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) prior to osimertinib dispensing at each visit

i. **Only applicable to patients receiving AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period**: Serum or plasma clinical chemistry (including LFT monitoring) and haematology should be performed if clinically indicated.

j. **Only applicable to patients receiving AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period**: ECHO/MUGA scans must be performed at the Week 12 and Week 24 visits.

k. Scan(s) should comprise the chest and abdomen (including adrenal glands and liver).

l. First post-surgical scan to be performed at Week 24, and thereafter at every visit timepoint in the EFS follow-up period (see footnote b).

m. Questionnaires will be completed at Adjuvant IP-osimertinib treatment decision visit, Week 12, Week 24, and then Q24 weeks until Week 264 and then every 48 weeks thereafter, or until disease recurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised.

n. Sites are to review if a hospital admission has been made since the last visit; if so, then HOSPAD should be completed. This module should be completed whenever the patient has attended or been admitted to the hospital (ie, each hospital admission, outpatient, or emergency room attendance encountered). It excludes routine follow-up clinic visits.

o. Optional sample in China. Samples will only be collected and analysed in China after approval by relevant local authorities.

p. AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period is not considered subsequent anticancer therapy.

q. In patients with known HIV infection that is well controlled, the patient's viral RNA load and CD4+ cell count should be monitored per local SoC (eg, every 3 months).

r. Not applicable in China.

s. Optional tumour FFPE tissue sample for exploratory analysis may be collected beyond the ± 14 days' time window as long as the sample is collected prior to the start of the next anti-cancer therapy.

t. To be collected prior to the initiation of adjuvant IP osimertinib, ideally on the same day, but may be collected up to 7 days prior to this visit.

u. Magnetic resonance imaging/contrast CT scans of the brain must also be conducted at recurrence.

2 INTRODUCTION

2.1 Study rationale

While the primary treatment for early-stage resectable non-small cell lung cancer (NSCLC) (Stages I to III) is curative surgery, the prognosis for patients treated with surgery alone remains poor. Patients with pathologic stage IIA NSCLC have 65% probability of survival at 60 months, which is reduced to 41% for the stage IIIA NSCLC (8th edition staging) (Goldstraw et al 2016).

In this treatment setting, there are numerous factors that make neoadjuvant therapy advantageous: earlier treatment of micrometastatic disease, reduction in tumour burden, evaluation of tumour sensitivity in vivo, prevention of tumour seeding at the time of surgery, and possible improved compliance with therapy (Farray et al 2005, Felip et al 2010).

According to National Comprehensive Cancer Network (NCCN) guidelines, chemotherapy is the only recommended neoadjuvant treatment for stage II- IIIB NSCLC patients (regardless of epidermal growth factor receptor [EGFR] mutation status), and whilst a number of studies have demonstrated encouraging results relating to the clinical benefit of neoadjuvant chemotherapy in early-stage NSCLC (eg. improvements in progression-free survival [PFS] and overall survival [OS]) (Pisters et al 2010, Scagliotti et al 2012, Song et al 2010, NSCLC Meta-analysis Collaborative Group 2014), further improvement is still needed.

Consequently, whilst there are currently no approved EGFR-tyrosine kinase inhibitor (TKI) therapies for use in the neoadjuvant treatment setting in EGFR mutation-positive (EGFRm) patients, recent evidence has been obtained that indicates that EGFR-TKI treatments (ie, gefitinib, erlotinib or afatinib) when given in the neoadjuvant setting can achieve clinically meaningful results in EGFRm NSCLC patients, in terms of both tumour response (pathological response and objective response) and survival (Zhong et al 2018a, Xiong et al 2018, Zhong et al 2015, Sequist et al 2018, Zhong et al 2018b, Lim et al 2009). Given the positive preliminary data obtained in EGFR-TKI targeted therapies in the early disease setting, and considering the compelling data in favour of osimertinib in the advanced treatment setting when compared with standard-of-care (SoC) chemotherapy (AURA3 study; Mok et al 2017) and against SoC EGFR-TKI treatments (erlotinib and gefitinib) in the first-line setting (FLAURA study; Soria et al 2018, Ramalingam et al 2019), there is a strong rationale to suggest that osimertinib may provide clinical benefit in the neoadjuvant treatment setting for EGFRm patients.

Therefore, in this Phase III study, the administration of osimertinib (either alone or in combination with chemotherapy) prior to surgery will be investigated to determine if this therapy regimen can improve activity and therefore long-term clinical outcomes for patients with resectable Stages II and IIIB NSCLC.

2.2 Background

2.2.1 Non-small cell lung cancer

Lung cancer has been the most common cancer in the world for several decades, with an estimated 2.09 million new cases in 2018, representing 11.6% of all new cancers. It was also the most common cause of death from cancer, with 1.76 million deaths (18.4% of all deaths) from lung cancer cases (GLOBOCAN 2018). NSCLC represents approximately 80% to 85% of all lung cancers (Howlader et al 2017), and despite advances in the diagnosis, imaging, staging, and treatment of NSCLC, the estimated 5-year overall survival rate for patients in Europe and the United States (US) continues to be low (11% and 17%, respectively; Pisters and LeChevalier 2005, D'Addario et al 2010).

For early-stage NSCLC (stages I to III) the prognosis for patients remains poor, with patients with pathologic stage IIA NSCLC have 65% probability of survival at 60 months, reduced to 41% for stage IIIA (8th edition staging) (Goldstraw et al 2016).

2.2.2 Early-stage NSCLC treatment options and unmet medical need

For early-stage NSCLC, primarily patients with stage I-II disease, although also for a significant proportion of patients with clinical stage IIIA and select IIIB disease, surgical resection remains the best curative option in those whose performance status allows (Lang-Lazdunski 2013). Whilst currently only approximately 30% of patients that present with Stages I to III lung cancer are suitable for surgical resection (Datta and Lahiri 2003), this percentage is expected to increase as a result of the implementation of lung cancer screening (The National Lung Screening Trial Research Team 2011).

Whilst surgery is considered to be a curative treatment option in early stage disease, it is acknowledged that despite recent advancements in thoracic anaesthesia, perioperative medicine and surgical techniques, which now allow patients with significant cardiopulmonary comorbidities to undergo lung resections routinely (Ceppa et al 2012), survival rates of NSCLC still remain low, which has largely been attributed to a tendency of patients to experience distant metastases over time (Chiari et al 2018). Furthermore, the role of surgery in patients with N2 disease remains controversial, with evidence suggesting that the long-term clinical benefit of surgical intervention in patients with N2 disease is negligible (Albain et al 2009, Van Meerbeeck et al 2007). However, in this patient population, there is evidence that downstaging with neoadjuvant therapy followed by surgery can lead to increased long-term survival (Bueno et al 2000).

With these factors in mind, the administration of neoadjuvant treatment prior to surgery forms part of the recommended NSCLC NCCN treatment guidelines, particularly for patients with Stage IIIA and IIIB/N2 disease. For patients who are considered suitable for neoadjuvant therapy, platinum-based doublet chemotherapy is the accepted SoC, with a number of studies

demonstrating the clinical benefit of neoadjuvant chemotherapy in early-stage NSCLC (Pisters et al 2010, Scagliotti et al 2012, Felip et al 2010), and a meta-analysis of 15 randomised clinical trials (stage I-III NSCLC; from 1985 to 2007) demonstrating an OS benefit for neoadjuvant chemotherapy (hazard ratio [HR] = 0.84; 95% confidence interval [CI]: 0.77 - 0.92; p = 0.0001), with an absolute survival improvement of 5% at 5 years (NSCLC Meta-analysis Collaborative Group 2014). It is acknowledged, in the earliest stages of disease, that the administration of preoperative treatment may delay potentially curative surgery and come at a cost of increased toxicity; however, it is the standard recommendation when surgical resection is planned in Stage III disease. Nevertheless, current evidence suggests that neoadjuvant or adjuvant chemotherapy in NSCLC is associated with only a modest improvement in absolute survival (approximately 5% in 5-year OS) versus surgery alone (Burdett et al 2007, Song et al 2010, NSCLC Meta-analysis Collaborative Group 2014).

Considering the relatively modest improvement in overall survival observed with perioperative chemotherapy treatment, there remains a significant unmet need for the development of efficient therapies that will help improve the prognosis of patients diagnosed with early-stage NSCLC.

2.2.3 Targeted molecular therapies in NSCLC

The investigation of treatments which target tumours driven by specific gene mutations (ie, EGFR, ALK, etc.) in the NSCLC neoadjuvant setting has become of increasing interest to the medical community, when used both in combination with chemotherapy or as monotherapy (Blumenthal et al 2018), and targeted molecular therapies have been shown to produce response rates that reliably exceed 50% with decreased toxicities compared to cytotoxic chemotherapies (Mayekar et al 2017).

In NSCLC patients whose tumours are EGFRm, EFGR-TKIs are considered the SoC in cases of advanced disease, with studies of osimertinib for the treatment of advanced NSCLC providing compelling data in support of clinically meaningful effects on PFS, duration of response, tumour shrinkage, and OS, when compared with other EGFR-TKI treatments in the first-line treatment setting (Soria et al 2018, Ramalingam et al 2019), and when compared to platinum-based chemotherapy in the second-line or greater setting (Mok et al 2017).

2.2.3.1 EGFR TKI treatments in early-stage NSCLC

Whilst there are currently no approved neoadjuvant or adjuvant treatments for the EGFRm NSCLC selected population, studies of neoadjuvant EGFR-TKI treatments in early-stage NSCLC have shown promising results in efficacy endpoints:

- In a recent study of 19 neoadjuvant patients with stage IIIA-N2 NSCLC who received erlotinib, 21.1% of patients demonstrated pathological downstaging following treatment, with an objective response rate (ORR) of 42.1%. Overall, 89.5% (17/19) of patients

achieved disease control, with a 10.3-month median disease-free survival among patients who underwent surgery (n=14). Among the 19 patients who received neoadjuvant therapy, median PFS and overall survival were 11.2 and 51.6 months, respectively (Xiong et al 2018).

- A study of 24 patients with IIIA-N2 NSCLC who received neoadjuvant treatment with either erlotinib or gemcitabine/carboplatin (GC), stratified by EGFR mutation status, demonstrated an ORR of 41.7 %, and a PFS and OS of 7.9 and 23.2 months, respectively, in the overall study population. The response rate was 58.3% for the erlotinib arm with mutant EGFR and 25.0% for the gemcitabine/carboplatin arm with wild type EGFR. Median PFS was 6.9 months versus 9.0 months, respectively. Median OS was 14.5 months for the erlotinib arm and 28.1 months for the GC arm (P = 0.201) (Zhong et al 2015).

- In study CTONG1103, which investigated the efficacy of erlotinib compared to gemcitabine plus cisplatin as neoadjuvant/adjuvant treatment in 72 patients, a major pathological response (MPR) rate of 10.7% with erlotinib versus 0% with chemotherapy prior to surgery was demonstrated, with lymph node downstaging reported in 13% in the erlotinib group and 4.2% in the chemotherapy group (Zhong et al 2018b).

- In the neoadjuvant afatinib ASCENT study, 13 stage III EGFRm patients were treated with afatinib for 2 months followed by concurrent chemoradiation (CRT) with cisplatin + pemetrexed. Following afatinib treatment, the ORR was 69%. Following CRT, 7 patients proceeded to surgery, with 4 patients reporting an MPR, and 1 patient reporting a pathological complete response (pCR) (Sequist et al 2018).

It is noted however that these data are based on limited populations sizes that are non-homogeneous for stage, and which involved the administration of possible confounding therapies (e.g. radiotherapy) (Chen et al 2018). No safety signal has been identified in relation to the use of EGFR-TKI therapies specifically in the neoadjuvant setting. In an ongoing Phase II study of neoadjuvant afatinib given with chemoradiation and surgery for stage III EGFRm NSCLC, CTCAE Grade 3/4 toxicities were in line with the existing safety profile expected with EGFR-TKI and chemotherapy treatments (rash, diarrhoea, esophagitis, nausea, pneumonitis and febrile neutropenia) (ASCENT study; Sequist et al 2018). In a further Phase II study of erlotinib given as neoadjuvant therapy, erlotinib was reported to be well tolerated.

There is no clear evidence that combination treatment of EGFR-TKIs with chemotherapy in EGFRm advanced NSCLC increases the incidence of toxicity events (Giaccone et al 2004, Herbst et al 2004, Herbst et al 2005, Gatzemeier et al 2007); however in studies of EGFR-TKIs given with or without pemetrexed-based chemotherapy, haematological toxicities were reported more frequently in patients receiving combination therapy compared with EGFR-TKI therapy alone (Nakamura et al 2018, Cheng et al 2016, Dudnik et al 2018, Han et al 2017, Oizumi et al 2018, Sugawara et al 2015, Yang et al 2018, Yoshimura et al 2015).

2.2.4 Osimertinib

Activation of EGFR-TKI triggers a cascade of intracellular downstream signalling events affecting cell proliferation, survival, angiogenesis, and potentially metastases. Selective inhibition of EGFR tyrosine kinase has demonstrated clinical benefit in approximately 70% of patients with advanced NSCLC harbouring activating-mutations in EGFR, the majority of which are also sensitising towards EGFR TKIs inhibition (the most common being deletions in the exon 19 mutation [Ex19del] and L858R, described collectively as EGFRm).

Osimertinib is an oral, third generation, irreversible EGFR-TKI that potently and selectively inhibits EGFR harbouring EGFRm and EGFR T790M mutations over wild-type EGFR, and has demonstrated clinical activity in NSCLC central nervous system (CNS) metastases.

Consistent with the designed pharmacological profile, osimertinib has demonstrated clinical benefit in the advanced treatment setting when compared with SoC chemotherapy (AURA3 study; Mok et al 2017) and against SoC EGFR-TKI treatments (erlotinib and gefitinib) in the first-line setting (FLAURA study; Soria et al 2018, Ramalingam et al 2019). Consequently, osimertinib is approved globally for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR Ex19del or L858R substitution mutations, and for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR-TKI therapy.

In osimertinib clinical studies in the metastatic setting, time to response to osimertinib treatment was very short, with most responses are observed at the time of the first RECIST (Response Evaluation Criteria in Solid Tumours) scan (week 6). Furthermore, early separation of PFS Kaplan-Meier (KM) curves in the FLAURA study adds encouraging data to suggest that osimertinib provides a quick and meaningful, response for early control of tumour cells.

In the ADAURA phase III trial, for osimertinib in the adjuvant treatment of patients with stage IB, II and IIIA (TNM edition 7) NSCLC with complete tumour resection, was recently unblinded early following a recommendation from the Independent Data Monitoring Committee (IDMC) based on its determination of overwhelming efficacy, compared to placebo. This was the first targeted agent in a global trial to show statistically significant and clinically meaningful improvement of DFS in adjuvant treatment of NSCLC patients following surgery. The overall HR was 0.21 (95% CI: 0.16, 0.28; $p<0.0001$), with osimertinib vs placebo DFS rates at 2 years of 89% and 53%, respectively (Herbst et al 2020). A consistent improvement in DFS was seen regardless of whether patients had received prior adjuvant chemotherapy. DFS benefit was also observed across the stages, with the HR in stage IB patients of 0.50 (95% CI: 0.25, 0.96). Immature OS (4.3% maturity) showed encouraging survival favouring osimertinib (Herbst et al 2020). The safety profile was

consistent with the known osimertinib safety profile, with no new safety concerns raised by the IDMC.

The data from this trial provide compelling evidence of the efficacy of osimertinib in the adjuvant setting for EGFRm positive NCSLC patients. Osimertinib will therefore be made available to all patients as adjuvant treatment in this study, if it is the physicians' choice of treatment post-surgery.

The AURA and FLAURA studies' and CNS efficacy data provide increased confidence that osimertinib treatment in the neoadjuvant setting, has the potential for early control of micrometastases (i.e. prior to surgery) to delay or prevent recurrence and thus provide long-term benefit, in conjunction with optimal care post-surgery.

To date, osimertinib has been administered to more than 10,000 patients as part of completed and ongoing clinical studies. Refer to the current osimertinib Investigator's Brochure (IB) for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK). A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of osimertinib is also provided in the IB.

2.2.4.1 Osimertinib in early-stage NSCLC

Currently, the role of osimertinib and other EGFR-TKI agents as neoadjuvant monotherapy in early-stage NSCLC with EGFR activating mutations has not been established; however preliminary findings from a Phase II study of neoadjuvant osimertinib in surgically resectable NSCLC (n=5 patients) indicated that 1-2 months of neoadjuvant treatment was well tolerated (with no serious adverse events [SAEs] reported), with a 100% disease control rate (unconfirmed radiographic partial response in 3 patients [60% ORR] and stable disease in 2 patients) (Rotow et al 2019); providing promising evidence of the role of EGFR TKI therapies in early-stage NSCLC.

Further to these data, AstraZeneca is also exploring osimertinib activity in earlier stage disease in 2 ongoing studies: ADAURA, from which the preliminary results are described above, and LAURA, investigating adjuvant osimertinib versus placebo in unresectable stage III patients following definitive chemoradiotherapy.

2.2.5 Osimertinib in combination with chemotherapy

The use of combination chemotherapy is a mainstay of oncology therapy, irrespective of biomarker status. The goal of combination chemotherapy is to utilise agents that affect cancer cells by different mechanisms, thus reducing the risk of developing resistance.

Currently, osimertinib is being investigated in an ongoing clinical study in combination with platinum plus pemetrexed chemotherapy as a first-line treatment in patients with EGFRm

locally advanced or metastatic NSCLC (Study D5169C00001 [FLAURA2]; see further details in Section 2.3.2.2).

2.2.6 Baseline clinico-pathological characteristics

The following baseline clinico-pathological characteristics/factors could be clinically relevant to the target study population of interest for this study: disease stage, EGFR mutation type, race, and smoking status.

These may be recorded and could be included as part of routine monitoring throughout enrolment of the study. Unexpected variations could be evaluated by AstraZeneca (see Appendix A).

2.3 Benefit/risk assessment

See Section 9.5.1 and Appendix A for information regarding the Independent Data Monitoring Committee (IDMC).

2.3.1 Potential benefits

Whilst there can be no certainty of clinical benefits of osimertinib either alone or in combination with chemotherapy for patients in neoadjuvant setting, there is strong biological rationale for treatment of EGFRm patients in the neoadjuvant setting, as targeted therapy has been shown to be more effective than systemic cytotoxic therapy in the metastatic setting. For osimertinib, this was illustrated in the AURA3 study, which demonstrated a median PFS of 10.1 months (95% CI: 8.3, 12.3) in the osimertinib arm compared with 4.4 months (95% CI: 4.2, 5.6) in the chemotherapy arm (HR 0.30 [95% CI: 0.23, 0.41; p-value <0.001]) at data cut-off date of 15 April 2016 (DCO1). The high response rate and early separation of the KM PFS curves illustrate a quick response to osimertinib treatment in the majority of patients, which manifests in a durable response for long-term benefit. Osimertinib has also demonstrated benefit over first-generation EGFR-TKIs in the first-line setting in the FLAURA study, with the final analysis of OS data (DCO2 [25 June 2019]; 57.7% maturity) demonstrating a statistically significant and clinically meaningful improvement in OS for patients on osimertinib compared to standard of care EGFR-TKI treatment (HR 0.799 [95% CI: 0.6409, 0.9963, p-value = 0.0462]).

Further to this, both the AURA3 (osimertinib versus chemotherapy) and FLAURA (osimertinib versus SoC EGFR TKI) studies have demonstrated clinical CNS activity, with clinically meaningful improvement in CNS PFS in the osimertinib arm compared to the comparator arms (which was statistically significant in the FLAURA study). Following surgery in NSCLC, recurrence of disease in the brain has been reported in approximately 20% of patients, with a poorer prognosis reported for these patients. Consequently, CNS activity is of clinical importance in prevention of disease recurrence at distant sites, including the brain (Torok et al 2017, Choi et al 2013, Lou et al 2013, Demicheli et al 2012).

Factors that may contribute to the benefit of osimertinib over SoC therapies include its irreversible binding to the EGFR, improved penetration of the blood-brain barrier, effectiveness in tumours with T790M mutation, and a margin to wild-type EGFR; which give a wider therapeutic margin to provide a sustained response to the therapy, prevention of resistance due to T790M, and reduction of CNS metastases. The activity of osimertinib in the metastatic setting has been compelling and consistent across the clinical development programme, from the durable responses seen in the Phase I and II studies through to clinically meaningful and statistically significant benefit compared to SoC chemotherapy in the second line setting and EGFR-TKI SoC in the first-line setting in PFS. It is expected that these beneficial traits will also translate to benefit in the neoadjuvant setting by providing a high response rate in the local tumour, and activity against micrometastases to prevent distant recurrence of the disease.

The combination of osimertinib with chemotherapy may provide further benefit by combining a cytotoxic compound with a targeted therapy to increase the likelihood of eliminating cancer clones not eradicated by osimertinib, to prevent disease recurrence and extend survival.

There is growing evidence of increased benefit of this combination in advanced EGFRm NSCLC, particularly in a recently published study conducted in Japan, in which the addition of carboplatin and pemetrexed to gefitinib as first-line treatment of patients with untreated advanced EGFRm NSCLC markedly improved the PFS and OS of patients, with an acceptable toxicity profile (Nakamura et al 2018, Seike et al 2018, Hosomi et al 2020). In addition, data from 4 prospective Phase II studies (2 randomised, 2 single arm) of gefitinib in combination with pemetrexed monotherapy or carboplatin/ pemetrexed doublet therapy followed by pemetrexed maintenance and a retrospective study of erlotinib with chemotherapy (predominantly platinum/pemetrexed), further support the concept of adding chemotherapy to EGFR-TKI therapy in the treatment of patients with EGFRm NSCLC (Cheng et al 2016, Dudnik et al 2018, Han et al 2017, Oizumi et al 2018, Sugawara et al 2015, Yang et al 2018, Yoshimura et al 2015).

2.3.2 Overall risks

2.3.2.1 Osimertinib

The tolerability profile of osimertinib when given as monotherapy is well characterised and suitable for long term dosing. In a pooled dataset that incorporated data from 1142 patients with advanced EGFRm NSCLC who received 80 mg osimertinib in all lines of therapy (first-, second-, and ≥third-line) in pivotal and supportive Phase I-III studies, the median duration of osimertinib therapy was 12.9 months (mean, 13.9 months; range, <0.1 – 40.1 months). In this pooled dataset, adverse drug reactions (ADRs) were mostly mild to moderate in severity (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 or 2), manageable by standard medical practice, and reversible. The most commonly reported ADRs in this dataset were diarrhoea (49%) and rash (47%). Other EGFR-TKI ADRs were typical of the class

effects of EGFR-TKIs, and comprised dry skin, pruritis, paronychia and stomatitis. CTCAE Grade 3 and Grade 4 adverse reactions occurred in 9.7% and 0.9% of patients, respectively. Dose reductions due to ADRs occurred in 2.1% of the patients and discontinuations due to ADR in 4.3% of patients.

Decreases from baseline in median values for platelets, neutrophils and leucocytes have been observed early in treatment with osimertinib. However, median haematological values appear to stabilise after the initial drop, with the majority of patients experiencing a single CTCAE grade change or no change in CTCAE grade. As would be expected with the small magnitude of these changes, no clinically significant sequelae in the population have been observed.

For information on all identified and potential risks with osimertinib, refer to the current version of the osimertinib IB.

Currently, the role of osimertinib and other EGFR-TKI agents as neoadjuvant monotherapy in early-stage NSCLC with EGFR activating mutations has not been established. Preliminary results from a Phase II study of 1-2 months neoadjuvant osimertinib in surgically resectable NSCLC (comprising data from 5 patients) indicated that neoadjuvant treatment was well tolerated (with no SAEs reported), and all patients proceeded to surgical resection without unscheduled delay or surgical complications (Rotow et al 2019).

2.3.2.1.1 Potential for neoadjuvant osimertinib to delay post-surgical wound healing

Clinical study data on EGFR-TKI associated impairment of wound healing and tissue repair are limited; and evidence of wound healing following preoperative EGFR-TKI largely constitutes individual case reports from pre-approval clinical trials and post-approval clinical use, which demonstrate that preoperative EGFR inhibitor use does not lead to postoperative complications or impairment of wound healing.

Given the role of EGF in cell regeneration, the lack of direct evidence of impairment of tissue repair in associated with exposure to EGFR TKI inhibitors suggests an involvement of redundant growth factor systems that replace reduced EGFR function. The potential for such impairment of the healing process is apparent with other TKI agents (such as axitinib, vandetanib and ponatinib); however, to date, the established first-generation EGFR TKIs (including erlotinib and gefitinib) are not associated with such potential risks. Both gefitinib and erlotinib have been used successfully in neoadjuvant and adjuvant clinical studies, with no drug-related surgical complications reported (Govindan et al 2003, Parikh and Ellis 2008, Shah et al 2014, Chaft et al 2011).

2.3.2.2 Osimertinib in combination with chemotherapy

There are no published data on the safety and tolerability of osimertinib in combination with chemotherapy in neoadjuvant setting, and there are limited published data of osimertinib in combination with chemotherapy in advanced NSCLC (Okada et al 2018, Tanaka et al 2019).

Nevertheless, there is a theoretical potential for overlapping toxicities between osimertinib and platinum/pemetrexed chemotherapy, notably haematological toxicities (which are established ADRs for all treatments) and delay to surgery due to adverse events (AEs).

With this in mind, in order to assess the safety and tolerability of osimertinib with cisplatin/carboplatin + pemetrexed and osimertinib, AstraZeneca have utilised data from the safety run-in phase of the ongoing FLAURA2 study to assess the safety profile of the chemotherapy plus osimertinib combination. The FLAURA2 study is a global phase III, open-label, randomized study of osimertinib with or without platinum plus pemetrexed chemotherapy conducted in patients with locally advanced or metastatic EGFRm (Ex19del and/or L858R) NSCLC who have not received any prior therapy for advanced disease. The safety run-in evaluated the safety and tolerability of the combination prior to commencing the randomised phase of the study. No new safety signals were identified from the review of data (N = 30) obtained in the safety run-in, and the study has progressed to the randomised phase without modification.

2.3.2.3 Potential for overlapping/additive haematological toxicities

Platinum-based agents and pemetrexed are associated with myelosuppression, with carboplatin associated with a higher incidence of severe thrombocytopenia than cisplatin (Ardizzoni et al 2007). Therefore, given that decreases from baseline in median values for platelets, neutrophils, lymphocytes and leukocytes have been observed early in treatment with osimertinib, there is a theoretical risk of overlapping haematological toxicities in patients receiving osimertinib + chemotherapy combination therapy.

In a retrospective analysis of patients with advanced EGFRm NSCLC treated off-label with concurrent chemotherapy and osimertinib, the majority of reported AEs were related to laboratory abnormalities (eg. neutropenia, liver function test [LFT] elevations, anaemia), however CTCAE grade 3 toxicities were rare and reversible, and the authors concluded that osimertinib does not appear to add significant toxicity to the various chemotherapy regimens (Piotrowska et al 2018).

A further comparative study of osimertinib alone versus osimertinib plus carboplatin/pemetrexed in patients with EGFRm NSCLC is ongoing (TAKUMI Study LOGIK1604/NEJ032A), with an interim analysis demonstrating that the frequency of AEs in the combination arm was similar to that of previous studies of carboplatin/pemetrexed, with no evidence of increased toxicity from the addition of osimertinib and no new safety signals noted for osimertinib (Okada et al 2018). A further safety review of data from this study was subsequently performed in 2019 with no increase in haematological toxicities reported.

2.3.2.4 Potential for overlapping toxicities leading to a delay in surgery

A practical concern with a neoadjuvant treatment strategy is the potential for delay of definitive surgery, which has been associated with trend toward reduced survival (when

extending surgery to 3–6 weeks compared to 0–3 weeks post-end of neo-adjuvant treatment (Yalman 2017).

Due to the potential for overlapping toxicities (eg, haematological) may increase the risk of a delay in surgery, time to surgery of a maximum of 3-weeks in this study will ensure enough time to recovery from AEs experienced AEs towards the end of the neoadjuvant treatment cycles. In addition to this, minimizing the time to surgery of a maximum of three weeks might reduce the potential of clinically significant risk of accelerated disease progression or tumour flare (Chaft et al 2011).

2.3.2.5 Potential for other overlapping toxicities

Other potential overlapping toxicities include but are not limited to rash, diarrhoea, stomatitis and interstitial lung disease (ILD). In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed. ILD has also been observed in patients receiving carboplatin.

There is also the potential for overlapping toxicity with respect to effects on fertility. Based on studies in animals, male fertility and female fertility may be impaired by treatment with osimertinib. For further details see the osimertinib IB. Gonadal suppression resulting in amenorrhea or azoospermia may occur in patients receiving antineoplastic therapy and such effects may be irreversible. Moreover, chemotherapy can have genetically damaging effects. Guidance on contraception requirements and sperm donation is provided in Section 5.3.1 and Appendix E. Due to the possibility of platinum-based chemotherapy and pemetrexed treatment causing irreversible infertility, men allocated/randomized to receive osimertinib and chemotherapy are advised to seek counselling on sperm storage before starting treatment.

2.3.3 Benefit-risk summary

Based upon the available clinical safety data, the investigation of the potential therapeutic efficacy and safety of osimertinib administered either alone or in combination with SoC chemotherapy prior to surgery is acceptable in patients with early-stage, resectable NSCLC, and the overall benefit/risk assessment supports the proposed study design.

3 OBJECTIVES AND ENDPOINTS

Table 3 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 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 objective:	**Endpoints/variables:**
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	• Subgroup analysis of MPR, pCR and EFS for patients randomised by FNA versus tumour 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).

Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQoL 5 dimension, 5-level health state utility index; HRQoL, Health related quality of life; ILD, interstitial lung disease; OS, Overall survival; PRO, Patient-reported outcome; QLQ-C30, 30 item core quality of life questionnaire; SoC, Standard of care.

4 STUDY DESIGN

4.1 Overall 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 randomized 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 mainland China], and Chinese living in mainland China), and mutation type (Ex19del versus L858R).

The randomised treatment regimens are as follows:

- 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 1)

  or

- Osimertinib 80 mg QD + investigator's choice of chemotherapy (as above) (Arm 2)

  or

- Osimertinib 80 mg QD as monotherapy (Arm 3)

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

The primary endpoint is MPR. Secondary endpoints are pathological complete response (pCR), downstaging, EFS, DFS, OS, and patient reported outcomes. For details of all endpoints, see Section 3.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data at regular intervals throughout the study, including one planned interim analysis for MPR. See Section 9 for details of statistical methodology and analysis.

4.1.1 Pre-screening and screening period

Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

To optimise the screening process for patients, consent can be provided either in a 2-step process (pre-screening followed by main consent) or directly via the main consent form. Pre-screening informed consent includes mandatory consent for procedures, including the collection of baseline tumour samples and baseline plasma samples. The baseline tumour sample will be used to assess EGFR mutation status for the assignment of patients to the study. The baseline plasma sample will be used to advance diagnostic development for EGFR testing and track tumour molecular aberrations in the circulation but will not be used for study entry criteria.

All patients are also asked to provide consent (which is included in both the pre-screening and main patient informed consent form [ICF]) to supply a sample of their tumour (archived or newly acquired tumour tissue sample, or fine needle aspirate [FNA] sample[1]) and plasma sample for entry into this study.

Additionally, patients will be given the option to consent to genetic sampling (whole blood collection) in a separate ICF. Participation in genetic research is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

An enrolment number (E-code) is assigned to a patient upon signing the first ICF for study participation, whether this is the pre-screening or main ICF (see Section 6.3.1).

At pre-screening, before patients are asked to consent, the investigator should assess the patient to see if there is a reasonable expectation that the patient will meet the eligibility criteria of the core protocol based on the medical information available to the investigator. At

[1] An archived tissue or new biopsy specimen, when no archived tissue is available, is acceptable. Patients will only undergo tumour biopsy if it is considered a medically acceptable risk by the investigator. When archival or new FFPE tumour tissue biopsy is not available, FFPE FNA sample collected per SoC prior to or during screening is also acceptable.

screening, consenting participants are assessed to ensure that they meet study eligibility criteria (see Section 5.1 and 5.2). Demographic data and other characteristics will be recorded and will include date of birth or age, gender, smoking history, and race and/or ethnicity (according to local regulations).

Screening procedures will be performed according to the schedule of activities (SoA) in Table 1 (Screening period).

It is recommended that the screening assessments are performed in a stepwise process beginning with the confirmation of EGFR mutation status (however, to shorten patients' waiting time before allocation to and initiation of study treatment, patients will be given the choice to undergo main screening assessments in parallel to the central EGFR mutation assessment). Confirmation of EGFR mutation status (Ex19del and/or L858R) is to be obtained via a prospective central cobas® EGFR Mutation Test v2 (Roche Molecular Systems) in a tumour tissue sample with preserved tumour tissue architecture (eg, core needle biopsy), performed at screening. Enrolment based on a pre-existing EGFR-mutation positive tumour test result using either the cobas® EGFR Mutation Test v2 (tumour tissue sample) according to its instruction for use (IFU) obtained by a CLIA-certified or locally accredited laboratory, or the FoundationOne® CDx (F1CDx™; Foundation Medicine, Inc., tumour tissue or FNA sample) is also permitted, and a tumour tissue sample with preserved tumour tissue architecture should be provided (where available) for retrospective central confirmation using the cobas® EGFR Mutation Test v2 (central EGFR mutation status result not needed to proceed with patient randomisation in these cases).

In the case that neither tumour tissue sample with preserved tumour tissue architecture, nor pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx EGFR test result per IFU from a tumour sample is available, EGFR mutation status can be centrally confirmed, when permitted by AstraZeneca, in a tumour FFPE FNA sample collected per SoC prior to, or during, screening, using the Idylla™ EGFR Mutation Test. Provision of additional tumour FFPE FNA samples, if available, is requested for future confirmation testing using an FDA approved FNA test. The total number of tumour FFPE FNA slides required can be found in the Laboratory Manual. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment, and participants who are EGFR mutation negative or do not meet eligibility criteria must not be randomised into the study.

Prior to randomisation, all prospective patients must be staged according to Tumour-Node-Metastasis (TNM) classification (AJCC Cancer Staging Manual, 8th Edition). Pathological evaluation (via mediastinoscopy, endobronchial ultrasound [EBUS], EUS, or other technique) is also required for any patient with computed tomography (CT)-enlarged or positron emission tomography (PET)-positive mediastinal lymph nodes (see Section 6.1.3.2 for further guidance).

A whole-body ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scan plus contrast-enhanced CT (or magnetic resonance imaging [MRI] scan) of the chest and abdomen will be acquired at Baseline (Days -28 to -1) for disease staging and for use as a baseline assessment. A brain MRI (preferred over CT) or a brain CT post contrast will also be performed to rule out metastases. See Section 8.1.2 for further details of tumour imaging assessments. Radiological assessments and other clinical data obtained as SoC prior to consent may be used for the study, provided the assessments were obtained within 6 weeks of randomisation.

Once study eligibility is confirmed, patients may then be randomised. 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). Every effort should then be made to minimise the time between randomisation and starting study treatment, and therefore if a patient is randomised to a chemotherapy-containing treatment arm, pre-treatment should be started as soon as possible after randomisation, and will take place prior to the start of study treatment (see Table 1 – Screening period, and Section 6.1.1.2 for details).

4.1.2 Neoadjuvant period

During the neoadjuvant treatment period, patients will be evaluated on Cycle 1, Day 1 (C1D1), 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 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. Every effort should be made to complete 3 cycles of treatment; refer to Section 6.1.3.1 for further details. 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 (see Section 4.1.3 below). Osimertinib/placebo may be continued up to the date of surgery in all treatment arms, at the discretion of the Investigator. See Section 6.1 for further details of study treatments to be administered. Dose delays and/or modifications are permitted with all study treatments in the case of toxicity. See Section 8.5.5 for further details.

A study treatment discontinuation visit should be performed only for patients who prematurely discontinue 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(s). For patients who complete 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 Table 2 (Survival period) should be followed thereafter.

All patients will be requested to complete a Health-related Quality of Life (HRQoL) and Patient-Reported Outcome (PRO) questionnaires per the schedules descried in Table 1 and Table 2.

4.1.3 Surgery period

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

For patients who are to be administered osimertinib/placebo treatment (at the investigators discretion) beyond the end of Cycle 3 (D64+), a supplementary visit should be conducted on D64 (+3 days), which will comprise osimertinib/placebo dispensing and safety assessments (see Table 1 – Surgery period: C4 osimertinib /placebo visit, for details).

During the surgery period, the patient should undergo a surgical assessment visit prior to surgery (on D64 -1 to +21 days), which includes the assessment of surgical eligibility (see Section 6.1.3.1) and a follow-up whole-body ^{18}FDG-PET scan and contrast-enhanced CT scan of the chest and abdomen (including adrenal glands and liver).

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 surgical 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).

Surgery is expected to be conducted at the site per the SoC as prescribed for the patient, and may consist of lobectomy, sleeve resection, bilobectomy, or pneumonectomy, including hilar and mediastinal lymph node resection as determined by the multi-disciplinary team (MDT) at the treating site (consisting of at least a clinical oncologist, thoracic surgeon, radiologist, and pathologist); and it is expected that the surgery will completely remove the tumour(s). If surgery cannot be conducted at the site due to unavoidable logistic issues (eg, cancellation of surgeries at the site due to Covid-19 pandemic), the plan for surgery at an alternative site must be discussed with and approved by the AstraZeneca Study Clinical Lead. Tumour specimens collected during surgery will be sent to a centralised pathology laboratory to assess pathological response, ideally within 8 weeks after surgery (see Section 8.1.1 for details).

A Safety Follow-up visit should be conducted 28 days (+14 days) after surgery for patients who underwent resection, which may be completed via the telephone (see Table 1).

4.1.4 EFS follow-up period

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

Post-surgery, patients should receive optimal care, as defined by the investigator and/or MDT, and physicians are required to follow the most recent NCCN, ESMO, Pan-Asian adapted ESMO, or other internationally recognised guidelines while planning adjuvant treatment.

At the treating Investigator's discretion, osimertinib will be made available to patients by AstraZeneca for a maximum 3-year treatment period, or until disease recurrence. If (at the Investigator's discretion) patients are to receive AstraZeneca-supplied 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 Section 6.1.2.2 prior to starting adjuvant osimertinib.

Note that post-operative radiotherapy and chemotherapy are permitted prior to starting adjuvant osimertinib treatment. For patients that receive radiotherapy prior to adjuvant therapy, osimertinib may be provided with agreement from the Sponsor's study physician. Note that adjuvant osimertinib will not be permitted for patients that had a symptomatic radiation pneumonitis that required steroids, or a history of ILD prior to adjuvant start.

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 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, including additional details regarding osimertinib dispensing (if applicable, and at the discretion of the Investigator) and the additional assessments to be performed for patients receiving AstraZeneca-supplied adjuvant osimertinib, see Table 2 (EFS follow-up 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 visit, Week 12 and Week 24 post-surgery visits, and Q24 weeks until Week 264 post-surgery then every 48 weeks (±14 days) thereafter until disease recurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first).

4.1.5 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 5 years from surgery (or from date of last neoadjuvant treatment if no surgery is performed) in the last randomised patient; see Table 2 (Survival period).

4.2 Scientific rationale for study design

4.2.1 Rationale for study design

Arms 1 and 2 of the study (osimertinib plus chemotherapy, and chemotherapy alone) will be double-blinded and placebo-controlled. Arm 3 (osimertinib monotherapy) will be open label (sponsor-blinded). Arm 1 will include a placebo control for osimertinib, in order to avoid bias in study conduct and reporting between Arm 1 and Arm 2. The sponsor does not consider it to be ethically acceptable or feasible to provide a placebo control for chemotherapy, and therefore Arm 3 is not blinded.

4.2.2 Rationale for patient selection

The target patient population of Stage II, IIIA and select IIIB NSCLC was selected in order to ensure the inclusion of patients who are eligible for surgical resection, per NCCN Guidelines (NCCN NSCLC Guidelines 2020). Patient selection will be further based on EGFRm status (Ex19del and/or L858R) (see Section 4.1.1) in order that a patient population most likely to respond to osimertinib treatment, in line with current approved indications, is enrolled.

4.2.3 Rationale for primary endpoint

There is evidence within the published literature that advances in the treatment of early stage (Stages I to III) NSCLC have been minimal over the past decade (Arriagada et al 2004), which may in part be due to this length of time taken to obtain clinically meaningful results in the resectable NSCLC patient population by way of traditional validated study endpoints. Traditional endpoints (such as OS), whilst acknowledged as the gold-standard clinical benefit measure providing the most persuasive outcome of an oncological clinical trial in the metastatic setting, poses considerable problems when applied in an early disease setting and/or biomarker selected populations. This is due to the requirement for a larger sample size and protracted study durations in order to achieve adequate statistical power for the detection of a clinically meaningful treatment effect and make this an infeasible choice of endpoint for the current study. Further to this, study objectives differ in the (neo)adjuvant setting, as the

ultimate aim is to improve cure rate and survival or to decrease toxicity without compromising efficacy.

In order to expedite the process of bringing new and effective treatment options to patients with resectable NSCLC, recent publications (Wilson et al 2015, Blumenthal et al 2017, Blumenthal and Pazdur 2016) have advocated the use of surrogate endpoints, which provide a measure of the meaningful clinical benefit of an investigational product which is considered predictive of OS, and which have the potential to improve the efficiency of trials and expedite scientific advances in the current landscape of early-stages NSCLC treatment.

In relation to the current study, the planned study population (EGFRm positive stage II-III NSCLC) is very small: stage III lung cancer is estimated to affect around 100,000 patients in the G7 countries (US, France, Germany, Italy, Spain, the United Kingdom and Japan) in 2016, with the majority of these having unresectable disease (Kantar Health 2016). Stage II patients represent a very small proportion of lung cancer patients (Morgensztern et al 2010) and so will not add significantly to this number. Of this population, it is expected that approximately 50% to 60% in Asian patients and 15% to 20% in patients from the West will have EGFRm positive disease (Shi et al 2014, Wu et al 2014, Dogan et al 2012). Taking these data into account, the expected population of EGFRm positive Stage II-III resectable patients in the G7 countries is estimated to be <5000. As such, a large study in this population is deemed to be unfeasible, with any study presenting recruitment challenges and long recruitment timelines. Furthermore, there are currently studies ongoing that may impact the treatment landscape for patients with early-stage NSCLC (eg. the osimertinib ADAURA study, for which results are expected in 2022), and therefore the conduct of a study with a long-duration of data collection for the determination of a treatment effect may not be feasible as evolution in current medical practice is expected within the timeframe of such a study.

In this regard, the primary endpoint of MPR has been selected for use in the current study, which is defined as ≤10% residual viable tumour in the lung primary tumour after neoadjuvant treatment at the time of resection, as assessed per central pathology laboratory. This endpoint is considered to meet the criteria of a surrogate endpoint in NSCLC, as current research has demonstrated it strongly associates with improved survival, is reflective of treatment impact, and captures the magnitude of the treatment benefit on survival. Furthermore, data suggest that MPR is sufficient to demonstrate good clinical activity on the local tumour as a marker of distant activity (on micrometastases), which explains the correlation seen between MPR and OS (Cascone et al 2018, Pataer et al 2012, Chaft et al 2013, Hellmann et al 2014, Blumenthal et al 2018).

In this study, it is considered that positive data using MPR as a surrogate endpoint for OS, combined with the acceptable toxicity profile and the positive evidence of the long-term benefit of osimertinib treatment that has been obtained in metastatic treatment setting and will

be generated in the adjuvant setting, gives confidence in osimertinib as a viable neoadjuvant option for patients being treated with curative intent. Furthermore, it is proposed that EFS and OS data will also be collected (as secondary endpoints) to observe the long-term benefits of all treatment arms.

4.2.4 Rationale secondary efficacy endpoints

The secondary endpoints and their rationales are presented below.

4.2.4.1 pCR

It is acknowledged that, whilst pCR is a validated surrogate endpoint for other cancers (eg. breast) and may appear to be a more stringent endpoint than MPR; data for pCR are highly variable, and frequently very low quantitatively, making a comparison very difficult to evaluate. As such, in order to adequately power for clinically meaningful changes between arms, a very large trial would be required, which would not be feasible in a small patient population of early stage EGFRm NSCLC. Nevertheless, pCR is still of scientific and medical value, and has therefore been selected as a secondary endpoint to detect any trends observed, with the study powered for MPR as the primary endpoint.

4.2.4.2 EFS and DFS

EFS and DFS are validated endpoints in the curative setting, indicative of longer-term clinical benefit. However, powering for endpoints of EFS as a primary objective would require a large study and a very long timeline that is considered unfeasible for this patient population. EFS and DFS will therefore be collected as secondary endpoints to provide some evidence of long-term benefit of a pathological endpoint, which is of particular clinical importance.

EFS will not be powered for in this study but will be incorporated into the multiple testing procedure along with MPR. The further details are provided in Section 9.

4.2.4.3 OS

Overall survival is the most important endpoint to demonstrate clinical benefit; however, powering for an OS endpoint would require a very large study and a very long timeline, that is considered unfeasible for this patient population. Nevertheless, as OS is considered clinically important information, this is to be collected as a secondary endpoint.

4.2.4.4 Downstaging

Nodal involvement is correlated with poorer prognosis (Decaluwé et al 2009, Bueno et al 2000), and response to treatment in involved lymph nodes, as well as in the primary tumour, is considered to be an important clinical outcome, particularly in MDT assessment. Downstaging therefore provides important information on success of neoadjuvant treatment for surgeons, and also constitutes a potential surrogate endpoint for long-term benefit. As it is nodal involvement that is most linked with a worsening prognosis,

downstaging will primarily focus on nodal downstaging – ie, patients that are N2 at baseline downstaging to N1/N0 at the time of surgery; or patients that are N1 at baseline downstaging to N0 at the time of surgery.

4.3 Justification for dose

4.3.1 Osimertinib

4.3.1.1 Rationale for choice of osimertinib dose

The dose of osimertinib in this study is 80 mg, orally, QD, which is the approved dose for the treatment of both first-line and second-line or greater locally advanced or metastatic EGFRm NSCLC, and is the dose that is being evaluated in phase III trials in locally advanced, unresectable Stage III EGFRm NSCLC (LAURA) and in the adjuvant setting (ADAURA).

The justification of the use of this dose in the current study was based on a robust non-clinical and clinical data package, obtained from the review of data obtained in the osimertinib development programme to date. The initial selection of the 80 mg dose was based on data from the AURA Phase I study, which was designed to support a robust dose selection decision (Jänne et al 2012), and which demonstrated a positive benefit/risk profile that maximises clinical activity in patients with EGFRm NSCLC, while simultaneously minimising the incidence and severity of adverse reactions as well as dose modifications. Importantly, this dose ensured that patients receive a clinically active dose regardless of inter-patient variability and allows prescribers to reduce the dose should this be necessary. Consequently, 80 mg QD was selected as the recommended dose for the neoadjuvant EGFRm clinical programme.

4.3.1.2 Rationale for choice of neoadjuvant osimertinib treatment duration

For patients assigned to the chemotherapy combination arm, the duration of osimertinib treatment will match the chemotherapy treatment duration (ie, 9 weeks' osimertinib treatment duration, to match the total duration of 3 cycles of chemotherapy). For patients assigned to the osimertinib monotherapy arm, osimertinib will also be 9 weeks, to allow for direct comparison with the combination arm (ie, evaluation of the added component of chemotherapy in addition to osimertinib monotherapy). This consideration takes into account evidence of potential efficacy, time of delay to surgery, and potential toxicities that may impact surgery.

Based on clinical data in the metastatic setting, the majority of responses to osimertinib in the AURA and FLAURA studies occur by the time of the first RECIST scan (ie, by 6 weeks), indicating an early, meaningful impact on tumour cells. This is in contrast to a slower time to response observed for chemotherapy treatment. This is further substantiated with the early separation of PFS curves observed in both the AURA3 study (osimertinib versus SoC chemotherapy) and the FLAURA study (osimertinib versus SoC EGFR-TKIs). Whilst caution is advised in translating RECIST responses in the metastatic setting to the neoadjuvant setting, these data add confidence that osimertinib is likely to provide a meaningful tumour reduction

(and impact on micrometastases) in the neoadjuvant setting with a 9-week duration of treatment.

Previous neoadjuvant studies with EGFR-TKIs have studied treatment periods that have ranged from 3-9 weeks (Xiong et al 2018, Schaake et al 2012, Zhong et al 2018b, Aukema et al 2010). In order to maximise the benefit without an unacceptable delay to surgery, a 9-week neoadjuvant treatment period has been selected.

As there has been a documented phenomenon of tumour flare following cessation of EGFR-TKI treatment (Chaft et al 2011), there is a risk of tumour growth between the end of the 9-week treatment period and surgery. Surgery is therefore encouraged to take place as soon as is feasible following the end of the neoadjuvant treatment period, however for patients for whom a delay to surgery is necessary, continuation of osimertinib/placebo beyond 9 weeks until just prior to surgery is permitted (at the discretion of the Investigator), in order to minimise the period of time between osimertinib/placebo cessation and surgery.

4.3.2 Chemotherapy

4.3.2.1 Rationale for choice of neoadjuvant chemotherapy regimen and dose

The chemotherapy treatment regimen is Investigator choice of either carboplatin AUC5 + pemetrexed 500 mg/m^2, or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2.

This chemotherapy treatment regimen was chosen based on NCCN Guidelines for the treatment of NSCLC (NCCN NSCLC Guidelines 2020), which states that cisplatin (75mg/m^2 + pemetrexed 500mg/m^2 every 21 days) is the preferred neoadjuvant treatment option for non-squamous NSCLC; with carboplatin recommended as an alternative to cisplatin for patients who are unable to tolerate cisplatin treatment. It is noted that EGFRm positive NSCLC is predominantly non-squamous in histology. Although cisplatin-based regimens have been most extensively studied and serve as the standard, no consensus exists on the best drugs to combine with cisplatin, and there are no data to show that the use of regimens substituting carboplatin for cisplatin is equivalent in terms of efficacy or toxicity (Blumenthal et al 2018).

The NCCN Guidelines also provide a number of other chemotherapy options (eg. vinorelbine, etoposide, gemcitabine, docetaxel or pemetrexed), all of which have also been considered for use in this study from both a risk and a benefit perspective; however, in relation to benefit, there are limited data available to suggest a clear advantage of any of the recommended neoadjuvant chemotherapy regimens, and therefore the main consideration of the chemotherapy choice was based on the potential risks of combining with osimertinib.

In this regard, studies of adjuvant chemotherapy with cisplatin + pemetrexed versus cisplatin + vinorelbine in NSCLC patients have reported that the combination of cisplatin + pemetrexed resulted in better tolerability / less toxicity, and similar efficacy compared to the cisplatin + vinorelbine regimen (Kreuter et al 2013, Kenmotsu et al 2019). Pemetrexed was therefore

selected over the other recommended combinations due to its acceptable safety profile, and lower level of overlapping toxicities with the established safety profile of osimertinib (eg. haematotoxicities).

4.3.2.2 Rationale for neoadjuvant chemotherapy treatment duration

Patients assigned to a chemotherapy-containing arm will receive 3 cycles of chemotherapy (Q3W) alone or in combination with once daily osimertinib/placebo, followed by surgery. Patients assigned to osimertinib (as monotherapy or in combination) will receive a minimum of 9 weeks of once daily 80 mg treatment, which can be continued up to the day of surgery, at the discretion of the Investigator.

The factors taken into consideration for the proposed duration of neoadjuvant therapy were evidence of efficacy, time of delay to surgery, and potential toxicities that may impact surgery. In studies of chemotherapy in the neoadjuvant setting, there is clear evidence of efficacy from 3 cycles. A meta-analysis of 15 randomised control trials (stage I-III NSCLC; from 1985 to 2007), showed a benefit of neoadjuvant chemotherapy on survival, representing an absolute survival improvement of 5% at 5 years (NSCLC Meta-analysis Collaborative Group 2014). From the 15 trials in this meta-analysis, eight used 3 cycles of neoadjuvant chemotherapy, five used 2 cycles, and one used an unknown number of cycles. In another neoadjuvant study (Betticher et al 2006), 3 cycles of cisplatin plus docetaxel were administered followed by surgery in 90 stage IIIA N2 NSCLC patients. Median survival was 28 months (35 months in the 75 patients that underwent surgery) and demonstrated efficacy results that were amongst the best observed in this setting.

Furthermore, a randomised phase III study (Pisters et al 2010) showed similar efficacy in terms of OS (median of 41 months) with 3 cycles of carboplatin plus paclitaxel, and also reported a major response rate (partial or complete) of 41%, demonstrating that 3 cycles is sufficient for short-term surgical benefit. This study also demonstrated an association between MPR and long-term benefit.

Thus, there is clear evidence that 3 cycles of neoadjuvant chemotherapy are sufficient to provide both short-term (MPR) and long-term (OS) benefit to NSCLC patients.

4.4 End of study definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- Food and Drug Administration requirements define 2 completion dates:

- Primary Completion Date - the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
- Study Completion Date - is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the SoA (Table 1 and Table 2).

The study may be terminated at individual study sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. The entire study may be terminated due to futility, or if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings (either within this study or in any other study with osimertinib).

See Section 6.7 for details on patient management following the final data cut-off, as well as following study completion.

After the study is completed, study results will be disseminated as outlined in the guidelines in Appendix A 6.

5 STUDY POPULATION

The target population of interest in this study is patients with resectable, stage II to resectable IIIB, EGFRm (Ex19del and/or L858R) NSCLC.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomised to a study intervention. Under no circumstances may there be exceptions to this rule. Patients who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign the informed consent form. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.2.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, and analyses.

3 For patients who agree to the optional genetic testing, provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative (as allowed per local regulations).

The ICF process is described in Appendix A 3.

Age and Sex

4 Male or female, at least 18 years of age. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

Type of patient and disease characteristics

5 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]). See Section 6.1.3.2 for details of preoperative mediastinal lymph node staging (at screening).

6 Complete surgical resection of the primary NSCLC must be deemed achievable, as assessed by a MDT evaluation (which should include a thoracic surgeon, specialised in oncologic procedures).

7 Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 at enrolment, with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.

8 Adequate organ and marrow function as defined below:

- Haemoglobin: ≥9.0 g/dL*

- Absolute neutrophil count: ≥1.5 × 10^9/L*
- Platelet count: ≥100 × 10^9/L*

  * **Note**: The use of granulocyte colony stimulating factor (G-CSF) support, platelet transfusion and blood transfusions to meet these criteria is not permitted prior to randomisation.

- Serum bilirubin: ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (unconjugated hyperbilirubinemia), who will be allowed in consultation with their physician.
- ALT and AST: ≤2.5 × ULN.
- Creatinine clearance ≥50 mL/min calculated by Cockcroft and Gault equation (refer to Appendix H for appropriate calculation) or assessed by 24-hour urine creatinine.

9 Life expectancy of >6 months prior to randomisation.

Tumour sample requirements

10 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 (eg, T790M, G719X, Exon20 insertions, S768I and L861Q). See Section 4.1.1 and 8.7.1.1 for details of requirements on eligible EGFR testing.

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11 Female patients who are not abstinent (in line with the preferred and usual lifestyle choice of the patient) and intend to be sexually active with a male partner must be using highly effective contraceptive measures, and must have a negative pregnancy test prior to first dose of any study treatment if they are of child-bearing potential; or must have evidence of non-child-bearing potential by fulfilling 1 of the following criteria at screening:

Post-menopausal, defined as aged 50 years or more and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

Women under 50 years old would be considered as postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and have luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution

Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

Further information is available in Appendix E (Definition of Women of Childbearing Potential and Highly Effective Contraceptive Methods).

12 Male patients must be willing to use barrier contraception (see Section 5.3.1).

5.2 Exclusion criteria

Medical conditions

1 History of allogeneic organ transplantation

2 Any evidence of severe or uncontrolled systemic diseases (as judged by the Investigator), including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol; or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV; that is not well-controlled). Active infection will include any patients receiving intravenous treatment for infection; active hepatitis B infection will, at a minimum, include all patients who are Hepatitis B surface antigen positive based on serology assessment. Screening for chronic conditions is not required.

Participants with known HIV infection that is well controlled may be included. All of the following criteria are required to define an HIV infection that is well controlled: undetectable viral RNA load for 6 months, CD4+ count of >350, no history of AIDS-defining opportunistic infection within the past 12 months, and stable for at least 6 months on the same anti-HIV medications. If an HIV infection meets the above criteria, the subject's viral RNA load and CD4+ cell count should be monitored per local SoC (eg, every 3 months). Subjects should be tested for HIV prior to randomisation if required by local regulations or Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Refer to Section 5.3.3.

3 Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

4 History of another primary malignancy (including any known or suspected synchronous primary lung cancer), except for the following:

- Malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of investigational product (IP) and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo malignancy without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

- Any synchronous Stage IA primary lung cancer that is ≤2 cm and planned to be resected during surgery for the Stage II to IIIB N2 lung tumour.

5 History of active primary immunodeficiency.

6 Patients who have pre-operative radiotherapy treatment as part of their care plan.

7 Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib.

8 Mixed small cell and NSCLC histology.

9 Stages I, IIIB N3, IIIC, IVA, and IVB NSCLC.

10 T4 tumours infiltrating the great vessels, the carina, the trachea, the oesophagus, the heart, and/or the vertebral body; and/or any bulky N2 disease.

11 Patients who are candidates to undergo only segmentectomies or wedge resections.

12 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 electrolyte abnormalities* including:

- serum/plasma potassium <lower limit of normal (LLN),
- serum/plasma magnesium <LLN**,
- serum/plasma calcium <LLN**,
- heart failure, congenital long QT syndrome, family history of long QT syndrome, unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes (see Section 6.5.2 and Appendix G).

* **Note**: Correction of electrolyte abnormalities to within normal ranges can be performed during the screening period.

** **Note:** Calcium and magnesium levels may be adjusted for hypoalbuminemia, if applicable.

13 Currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

Prior/concomitant therapy

14 Prior treatment with any systemic anti-cancer therapy for NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug

15 Prior treatment with EGFR-TKI therapy

16 Current use of (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of cytochrome P450 (CYP) 3A4 (at least 3 weeks prior), see Appendix G

17 Any major surgical procedure (as defined by the Investigator) which occurred within 28 days prior to the first dose of IP. Procedures such as placement of vascular access, biopsy via mediastinoscopy or biopsy via video assisted thoracoscopic surgery (VATS) are permitted

Prior/concurrent clinical study experience

18 Involvement in the planning or conduct of the study (applies to AstraZeneca staff and staff at the study site)

19 Participation in another clinical study with an IP administered in the last 4 weeks

20 Previous IP assignment in the present study

21 Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

22 Prior randomization or treatment in a previous osimertinib clinical study regardless of treatment arm assignment

Other exclusions

23 Known allergy or hypersensitivity to any of the study drugs, study drug excipients, drugs with a similar chemical structure or class, or anaesthetics

24 Contraindication for pemetrexed and cisplatin/carboplatin according to local approved label e.g., use of a live vaccine within 30 days of randomisation

25 Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study

26 Exclusion criteria for participation in the optional genomic initiative component of the study include the following:

Previous allogeneic bone marrow transplant

Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection

5.3 Lifestyle restrictions

The restrictions described in this section apply while the patient is receiving study treatment and for the specified times before and after.

Restrictions relating to concomitant medications are described in Section 6.5.

5.3.1 Pregnancy

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

- Female patients of child-bearing potential who are not abstinent (in line with the preferred and usual lifestyle choice of the patient) and intend to be sexually active with a male partner must use acceptable methods of highly effective contraception from screening until at least 6 weeks after discontinuing osimertinib/placebo and at least 6 months after discontinuing platinum-based chemotherapy. Acceptable methods are provided Appendix E (Definition of Women of Childbearing Potential and Acceptable Highly Effective Contraceptive Methods). Note that a risk for an osimertinib-associated decreased exposure of hormonal contraceptives cannot be excluded.
- Male patients must use barrier contraceptives (ie, condoms) during sex with a female partner of child-bearing potential (including a pregnant partner) from the start of dosing until at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib/placebo. In addition, patients must refrain from donating sperm from the start of dosing until at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib/placebo.
- Due to the possibility of platinum-based chemotherapy and pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment (see Section 2.3).

5.3.2 Meals and dietary restrictions

Osimertinib can be taken without regard to food.

The use of any natural/herbal products or other "folk remedies" should be discouraged and in particular patients should avoid taking dietary supplements or herbal medicines with known strong inducers of CYP3A4 whenever feasible (see Section 6.5). The use of any natural/herbal products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications should be recorded in the electronic case report form (eCRF).

5.3.3 HIV infection

In patients with known HIV infection that is well controlled, the patient's viral RNA load and CD4+ cell count should be monitored per local SoC (eg, every 3 months). Patients should be tested for HIV prior to randomisation if required by local regulations or IRB/IEC. Antiviral treatment should be continued during study treatment per local physician.

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study, but do not meet the criteria for participation (see inclusion and exclusion criteria in Section 5.1 and Section 5.2). A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened, with the exception of patients with a central EGFR test negative result for Ex19del or L858R. Rescreened patients should use the same patient number assigned previously at the first time of screening via interactive voice/web response system (IVRS/IWRS). Rescreening should be documented so that its effect on study results, if any, can be assessed. Note: rescreening of a patient is only permitted once.

Patients who initially fail to qualify for the study based on safety laboratory test results (ie, clinical chemistry [including creatinine clearance] and haematology) or ECG results may have their laboratory value and ECG assessment retested 1 time within the 28-day screening period at the discretion of the Investigator. Retesting within the 28-day screening period does not constitute rescreening; however, if retesting falls outside of the 28-day screening period, it should be considered a rescreen.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to osimertinib, placebo, and chemotherapy (SoC; pemetrexed and either cisplatin or carboplatin).

6.1 Treatments administered

6.1.1 Investigational products

Study treatments are shown in Table 4. AstraZeneca will supply osimertinib and matching-placebo tablets for use in the neoadjuvant phase. If adjuvant osimertinib is to be prescribed in the EFS follow-up period (at the Investigator's discretion), AstraZeneca will supply treatment for a maximum 3-year period. In this scenario, osimertinib will continue to be regarded as a study treatment.

Chemotherapy (SoC) agents will be supplied locally. Under certain circumstances when local sourcing is not feasible, SoC chemotherapy may be supplied centrally through AstraZeneca for the neoadjuvant study period.

Selection of cisplatin or carboplatin is per Investigator’s choice. The investigational site should declare (in the IVRS/IWRS) their choice of chemotherapy for each patient prior to randomisation to cover the eventuality that the patient is randomised to one of the SoC chemotherapy treatment arms (Arm 1 or Arm 2). Randomisation will be made in IVRS/IWRS system as soon as all the eligibility criteria are met, as confirmed by the Investigator, and should be documented in the medical records.

If study treatment includes SoC chemotherapy, pre-treatment should be started as soon as possible after randomization and will take place prior to the start of study treatment as described in Table 1 and Section 6.1.1.2.

Dose modifications are described in Section 6.6.

Table 4 Study treatments

	Osimertinib	Placebo	Standard of Care [a]	
Study treatment name:	Osimertinib (AZD9291)	Osimertinib- matching placebo	Pemetrexed/ Cisplatin [b]	Pemetrexed/ Carboplatin [b]
Dosage formulation:	80 mg tablet for oral administration 40 mg tablet for oral administration	NA	As sourced locally	As sourced locally
Route of administration:	Oral	Oral	IV infusion	IV infusion
Dosing instructions:	**Neoadjuvant period:** Osimertinib 1 tablet of 80 mg QD. Treatment is to be started on Day 1 until Day 63; however, can be continued until the day of surgery, at the discretion of the Investigator. **EFS follow-up period:** Osimertinib 1 tablet of 80 mg QD for a maximum of 3-years, or until disease recurrence (as described in Section 6.1.1.1).	**Neoadjuvant period:** 1 tablet of matching placebo 80 mg QD. Treatment is to be started on Day 1 until Day 63; however, can be continued until the day of surgery, at the discretion of the Investigator.	Following appropriate pre-treatment (as described in Section 6.1.1.2.1 and Section 6.1.1.2.2), pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) are to be taken on Day 1 of every 3-week cycle for 3 cycles	Following appropriate pre-treatment (as described in Section 6.1.1.2.1 and Section 6.1.1.2.3), pemetrexed (500 mg/m^2) plus carboplatin (AUC5) are to be taken on Day 1 of every 3-week cycle for 3 cycles
Packaging and labelling:	Osimertinib will be provided in in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Osimertinib-matching placebo will be provided in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Pemetrexed and cisplatin will be sourced locally where country regulations allow.	Pemetrexed and carboplatin will be sourced locally where country regulations allow.
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Provider:	AstraZeneca	AstraZeneca	Sourced locally by site	Sourced locally by site

Abbreviations: AxMP, auxiliary medicinal product, AUC, Area under the curve; HDPE, High-density polyethylene; GMP, Good Manufacturing Practice; IMP, investigational medicinal product; NIMP, non-investigational medicinal product; QD, once daily

[a] Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally source the drug, which will be labelled with text translated to local language in accordance with regulatory guidelines.

[b] In the event of unfavourable tolerability, patients can switch from cisplatin to carboplatin therapy, and also from carboplatin to cisplatin at any point during the study (assuming eligibility for the switched therapy is met).

6.1.1.1 Osimertinib (AZD9291) or matching placebo dosing

In the neoadjuvant period, on D1 of each treatment cycle (C1-C3), sufficient osimertinib or matching placebo for the 3-week treatment period will be dispensed. For patients who are to be administered osimertinib/placebo treatment (at the investigators discretion) beyond the end of Cycle 3 (D64+), a supplementary visit should be conducted on D64 (+3 days), which will comprise osimertinib/placebo dispensing for the required duration prior to surgery. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Patients should swallow 1 tablet QD, commencing on C1D1. Tablets should be taken whole with water, with or without food.

If osimertinib is prescribed in the EFS follow-up period (at the discretion of the Investigator) and supplied by AstraZeneca, dispensing will occur at each study visit. In the EFS follow-up period, osimertinib will be provided in open-label bottles and will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

To allow for management of IP-related toxicities, the initial dose of osimertinib 80 mg QD can be reduced to 40 mg QD/placebo (see Section 6.6 and Section 8.5.5). Once the dose of osimertinib is reduced to 40 mg/placebo once per day, the patient will remain on the reduced dose until termination from study treatment. Re-challenge at 80 mg/placebo is not allowed in the neoadjuvant portion of the study.

Doses should be taken approximately 24 hours apart at the same time each day. Doses should not be missed. If a patient misses taking a scheduled dose, it is acceptable to take the dose within a window of 12 hours. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and the patient should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking the IP, he/she should not make up for this dose but should take the next dose at the scheduled time.

The reason for any missed dose should be documented in the source document.

Any change from the dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

Additional information about osimertinib may be found in the IB.

6.1.1.2 Chemotherapy dosing

The SoC chemotherapy agents for use in the neoadjuvant period will be locally sourced and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, which will be labelled with local language translated text in accordance with regulatory guidelines.

Pre-treatment for chemotherapy with folic acid, vitamin B12, and/or corticosteroids should be completed prior to osimertinib, cisplatin, carboplatin, and pemetrexed dosing according to the guidelines in Section 6.1.1.2.1 (pemetrexed), Section 6.1.1.2.2 (cisplatin), and Section 6.1.1.2.3 (carboplatin) below.

Anti-emetic premedication can be administered according to local standards of care; however, given the potential for an interaction between osimertinib and some antiemetic therapies with respect to prolongation of the QTc interval, additional guidance is provided in Section 6.5.2. Patients may also receive other additional supportive premedication / concomitant treatments according to local standards of care clinically or as indicated by the Investigator, in accordance with the information provided in Section 6.5.

For the osimertinib/placebo + chemotherapy treatment arm, osimertinib/placebo and chemotherapy dosing should begin on the same day, with osimertinib/placebo treatment administered first.

6.1.1.2.1 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes.

To reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 mcg) on a daily basis. Additionally, intramuscular injection of Vitamin B12 (1000 mcg or 1 mg) must be given.

- Folic Acid: At least 5 doses of folic acid should be taken during the 7 days preceding the first dose of pemetrexed. Folic acid dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

- Vitamin B12: Patients should also receive an intramuscular injection of vitamin B12 in the week preceding the first dose of pemetrexed. Subsequent vitamin B12 injections may be given on the same day as pemetrexed. Do not substitute oral vitamin B12 for intramuscular vitamin B12.

To reduce the incidence and severity of skin reactions, a corticosteroid must be given. The corticosteroid should be given over 3 days: the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.

6.1.1.2.2 Cisplatin

Cisplatin 75 mg/m^2 will be administered as an IV infusion according to local practice and prescribing information approximately 30 minutes after the pemetrexed infusion and should be immediately preceded and followed by hydration.

Patients who are receiving cisplatin are at increased risk of developing nephrotoxicity, ototoxicity, neuropathy, myelosuppression and nausea and vomiting and should be carefully monitored in accordance with local standards of care.

6.1.1.2.3 Carboplatin

Carboplatin AUC5 mg/mL·min will be administered as an IV infusion over 15-60 minutes, after the pemetrexed infusion, according to local practice and prescribing information.

Carboplatin dose is calculated using the Calvert formula, at a dose not to exceed 750 mg. Glomerular Filtration rate in the Calvert formula is estimated by calculated creatinine clearance using the Cockcroft-Gault Equation (Appendix H) or assessed by 24-hour urine creatinine.

Calvert Formula:

Total Dose (mg) = (target AUC) x (creatinine clearance + 25)

- The estimated glomerular filtration rate used in the Calvert formula should not exceed 125 mL/min.
- Maximum carboplatin dose (mg) = target AUC5 (mg/min.mL) x (125 + 25) = 5 x 150 mL/min = 750 mg

Patients who are receiving carboplatin are at increased risk of developing myelosuppression, nephrotoxicity and allergic reactions. In addition, ototoxicity and neuropathy have been observed. Patients should be carefully monitored in accordance with local standards of care.

6.1.2 Study treatment regimen and duration of treatment

6.1.2.1 Neoadjuvant period

All assigned treatment will be administered beginning on D1.

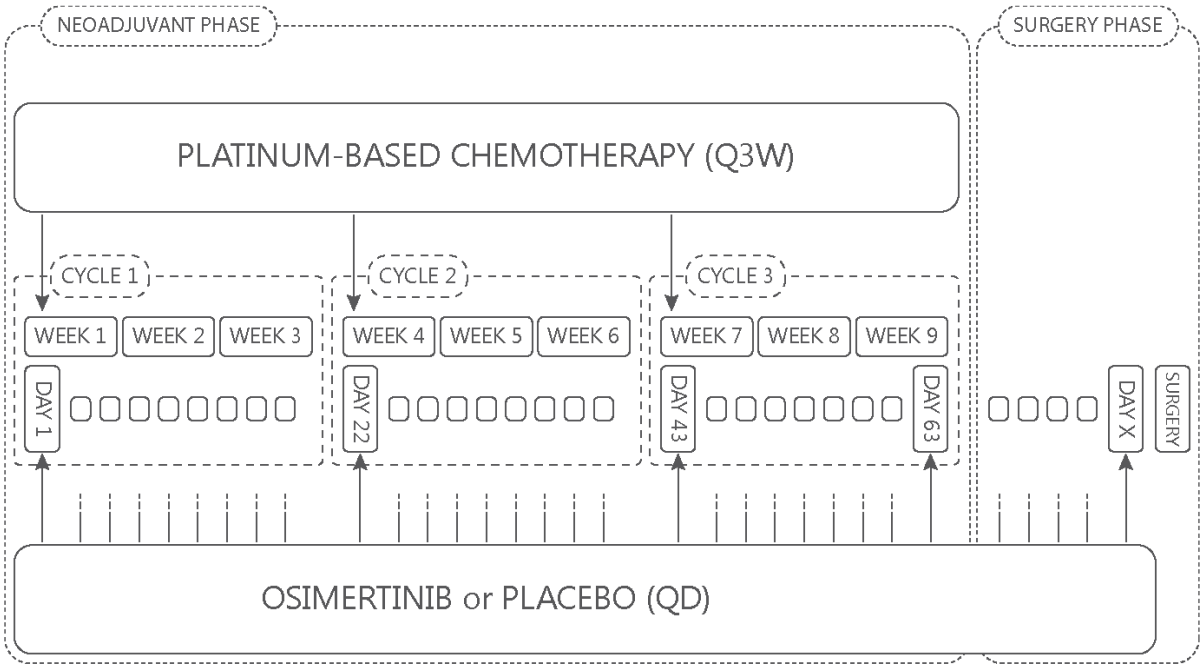
In the neoadjuvant period, patients assigned to a chemotherapy-containing arm (Arm 1 or Arm 2) will receive 3 cycles of chemotherapy Q3W in addition to QD osimertinib/placebo (Figure 2). Treatment with osimertinib/placebo may be continued until the day of surgery; unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion are met; see Section 7.1.

Patients assigned to the osimertinib monotherapy arm (Arm 3) will receive QD osimertinib treatment until the day of surgery (Figure 3); unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion are met; see Section 7.1.

Surgery is expected to occur as soon as possible between D64 (start of week 10, ie, the day following the end of SoC Cycle 3 for Arms 1 and 2; or end of week 9 for Arm 3) and D84 (end of week 12). In exceptional circumstances (and with prior agreement from the Sponsor's study physician) this surgical period may be extended by 1 additional week (to

end of week 13; ie, surgery must occur on or before Day 91 as counted from C1D1 independent of dosing delays or interruptions).

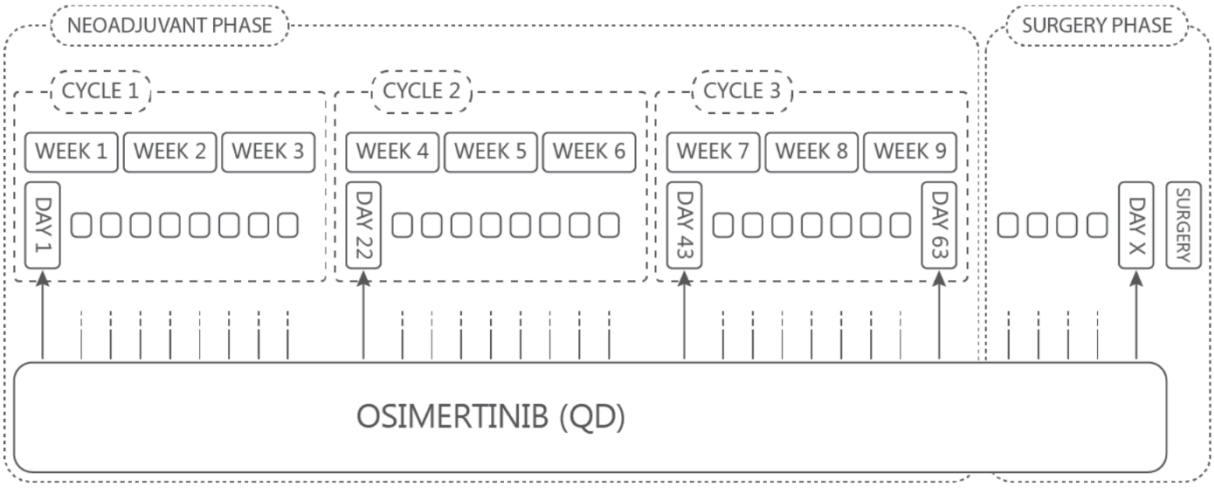
Figure 2 Dosing schedule of chemotherapy-containing treatment arms



Abbreviations: Q3W, Every 3 weeks; QD, Every day

Note: Choice of platinum-based chemotherapy (see Table 4) will be Investigator's discretion.

Figure 3 Dosing schedule of osimertinib monotherapy treatment arm



Abbreviations: QD, Every day

6.1.2.2 Adjuvant osimertinib during the EFS follow-up period

At the treating Investigators discretion, osimertinib 80 mg QD will be made available by AstraZeneca to patients entering the EFS follow-up period who underwent and completed

surgery for a maximum 3-year treatment period, or until unacceptable toxicity or disease recurrence.

If (at the Investigator's discretion) patients are to receive AstraZeneca-supplied osimertinib in the EFS follow-up period, this will be regarded as an IP, and the following inclusion and exclusion criteria relevant to initiation of adjuvant therapy must be met prior to commencing adjuvant treatment: Inclusion criteria 7, 8, 11, and 12, and Exclusion criteria 2, 3, 7, 12, 13, and 16 (see Section 5.1 and Section 5.2). Please note that for Inclusion criterion 8, creatinine clearance must be ≥30 mL/min calculated by Cockcroft-Gault equation (refer to Appendix H) or assessed by 24-hour urine creatinine.

Note that post-operative radiotherapy and chemotherapy are permitted prior to starting adjuvant osimertinib treatment. For patients that receive radiotherapy prior to adjuvant therapy, osimertinib may be provided with agreement from the Sponsor's study physician. Note that adjuvant osimertinib will not be permitted for patients that had a symptomatic radiation pneumonitis that required steroids, or a history of ILD prior to adjuvant start. If adjuvant osimertinib is to be prescribed in the EFS follow-up period, then treatment should commence no sooner than 4 weeks and no later than 12 weeks following surgery if no other post-operative treatment is given; within 26 weeks following surgery if post-operative chemotherapy is given; or within 4 weeks of the last dose of radiotherapy if post-operative radiotherapy is given.

Patients who required permanent discontinuation of osimertinib during neoadjuvant treatment with osimertinib monotherapy for any of the following adverse reactions will not be offered adjuvant osimertinib: Interstitial lung disease (ILD)/Pneumonitis, QTc interval prolongation with signs/symptoms of serious arrhythmia, Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks.

Patients who required permanent discontinuation of osimertinib/placebo during neoadjuvant treatment with osimertinib/placebo in combination with platinum/pemetrexed chemotherapy for any of the following adverse reactions will not be offered adjuvant osimertinib: Interstitial lung disease (ILD)/Pneumonitis, QTc interval prolongation with signs/symptoms of serious arrhythmia. Patients who required dose reduction of osimertinib/placebo during neoadjuvant treatment and patients who required permanent discontinuation of osimertinib/placebo because of a G3 or higher adverse reaction that does not improve to Grade 0-2 after withholding of osimertinib/placebo for up to 3 weeks, may be considered for osimertinib adjuvant therapy following discussion and agreement with the AstraZeneca study physician, if considered in the patient's best interest.

6.1.3 Surgery

6.1.3.1 Surgery eligibility

Patient eligibility for surgery must be assessed following neoadjuvant treatment (see Table 1 – Surgery period).

The determination of resectability, surgical staging, and pulmonary resection should be performed by a locally-certified thoracic surgeon who performs lung cancer surgery as a prominent part of his/her practice. The surgeons should actively participate in multidisciplinary discussions and meetings regarding patients within the study.

For the purposes of this study, resectability should be evaluated prior to inclusion into the study and prior to surgery and is defined by an expected R0 resection. N2 lymph nodes should not involve more than 3 stations and must be without evidence of bulky disease.

The surgery to be performed will be lobectomy, sleeve resection, bilobectomy, or pneumonectomy, including hilar and mediastinal lymph node resection, as determined by the attending surgeon based on the intraoperative findings.

The patient must be medically fit to tolerate the planned resection according to the guidelines.

At surgical assessment, all patients must meet **all** the following surgical eligibility criteria:

1. Complete surgical resection of the primary NSCLC must be deemed achievable, as assessed by an MDT evaluation.

2. Received 3 cycles of platinum-based chemotherapy concurrent with osimertinib or placebo, or 9 consecutive weeks of osimertinib monotherapy.

    - Surgery following receipt of less than 3 cycles of platinum-based chemotherapy will be permitted only if the patient experienced chemotherapy-related toxicities, and Investigators judge additional safety issues will be expected with additional cycles of chemotherapy. In such cases, if surgery is planned prior to D64, the patient must be discussed with the AstraZeneca Study Clinical Lead or delegate.

    - Surgery following receipt of less than 9 weeks of osimertinib/placebo treatment will be permitted only if the patient experienced treatment-related toxicities, and Investigators judge additional safety issues will be expected with additional treatment administration. In such cases, if surgery is planned prior to D64, the patient must be discussed with the Study Clinical Lead or delegate.

3. Surgery should happen between D64 and D84 (+7 days in exceptional circumstances and with the agreement of the Sponsor), counted from C1D1 independent of dosing delays or interruptions.

4. Patients must have recovered from all acute, reversible toxic effects from chemotherapy (excluding alopecia), osimertinib or placebo that could potentially adversely impact the surgical procedure or outcome according to the Investigator's judgement.

5. A contrast enhanced CT scan of chest and abdomen (including the entire liver and both adrenals) is required for tumour assessment and for surgical planning prior to surgery. A whole-body (base of skull to mid-thigh) ^{18}FDG-PET scan is also required prior to surgery in order to help identify mediastinal lymph node involvement, according to investigators judgement.

6. Patients must have adequate cardiac and lung function, according to the MDT assessment. A pre- or post-bronchodilator forced expiratory volume in 1 second (FEV1) of 1.0 L or >40% postoperative predicted value and diffusing capacity of the lungs for carbon monoxide (DLCO) >40% postoperative predicted value is recommended.

The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated. CT and PET used for staging should be within 30 days before proceeding with surgical evaluation (NCCN NSCLC Guidelines 2020).

6.1.3.2 Preoperative mediastinal lymph node staging (at screening)

Nodal assessment is critical to accurate staging for Inclusion Criterion 5 (see Section 5.1).

Mediastinal staging, which must be performed prior to neoadjuvant therapy, is very important, as it provides accurate information on the extent of the disease, guides the choice of treatment, and determines the patient's prognosis. Lymph node mapping is defined by The International Association for the Study of Lung Cancer (IASLC Staging Manual in Thoracic Oncology 2016) lymph node map. The European Society of Thoracic Surgeons guidelines (De Leyn et al 2014) on imaging, endoscopic, and surgical techniques for lymph nodes staging should be followed.

The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy, since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. Final determination of N-stage should be done by a multidisciplinary team, including a board-certified thoracic surgeon.

EBUS (± EUS) are additional techniques for minimally invasive pathologic mediastinal staging that are complementary to mediastinoscopy. When these modalities are employed, it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral lymph node involvement prior to a final treatment decision.

Requirements prior to study inclusion:

1. In case of CT-enlarged or PET-positive mediastinal lymph nodes (i.e. N2 disease), tissue confirmation is mandatory. Endosonography (endobronchial ultrasonography [EBUS]/oesophageal ultrasonography [EUS]) with FNA is the first choice (when available), since it is minimally invasive and has a high sensitivity to rule in/out

mediastinal nodal disease. If negative on EBUS but with high suspicion, surgical staging with nodal dissection or biopsy is indicated (video-assisted mediastinoscopy is the preferred choice, VATS is an alternative). The combined use of endoscopic staging and surgical staging results in the highest accuracy. All abnormal lymph nodes should be documented at study entry.

2. When there are no enlarged mediastinal lymph nodes on CT and when there is no uptake in lymph nodes on PET or PET–CT (cN0), patients can be included into the trial as cN0 without invasive mediastinal assessment. In addition, invasive mediastinal evaluation of patients with cN1 disease is not mandatory.

3. If pathologic mediastinal lymph node evaluation procedures were already performed as part of clinical practice at initial evaluation prior to signing consent, these can be used for screening purposes with consent of the patient.

   Patients with occult-positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal lymph node resection.

6.1.3.3 Pre-treatment risk assessment

The recommendations of the European Society for Medical Oncology (ESMO) for pre-treatment risk assessment should be followed. Overall, the cardiopulmonary fitness of the patient will determine the choice of treatment. Before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity. For cardiac assessment, use of recalibrated revised cardiac risk index (RCRI) is recommended. The RCRI includes a number of weighted factors, including ischemic heart disease, history of cerebrovascular disease, serum creatine >2 mg/dL, and planned pneumonectomy. Each factor is assigned a point value, and patients are grouped into classes based on the total number of points. If a patient has at least 3 weighted factors or any cardiac condition requiring medications, a newly suspected cardiac condition, or inability to climb 2 flights of stairs, then a cardiac consultation with non-invasive cardiac testing treatments should be performed according to American Heart Association/American College of Cardiology guidelines. If there is a need for coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention), then surgery should be postponed for 6 weeks or more. If ongoing cardiac care may continue, or any needed new medical interventions are instituted (ie, beta blockers, anticoagulants, or statins), then the patient may proceed with lung function tests.

Formal lung function testing should be undertaken to estimate postoperative lung function. For patients with FEV1 and DLCO values >80% of their predicted pulmonary function tests and no other major comorbidities, no further investigations are advised before surgical resection. For others, exercise testing and split lung function are recommended. In these patients, maximal oxygen consumption can be used to measure exercise capacity and

predict postoperative complications. Surgical resections is usually acceptable if the predicted postoperative FEV1 and DLCO values are >40%.

Comorbidities should be evaluated and optimized before surgery. In patients with limited pulmonary function due to emphysema, a lung volume reduction effect may be observed by resection of the lung cancer within emphysematous lung tissue (Postmus et al 2017).

6.1.3.4 Resection

The recommendations of ESMO and NCCN for the resectability of NSCLC must be followed.

Complete resection requires free resection margins, systematic node dissection (SND) or sampling, and the highest mediastinal node negative for tumour. The resection is defined as incomplete whenever there is involvement of resection margins, unremoved positive lymph nodes, or positive pleural or pericardial effusions. Dissection regarding lymph node stations and margin see Section 6.1.3.5 and Section 6.1.3.6.

Anatomic pulmonary resection is preferred for the majority of patients with NSCLC. Either open thoracotomy or VATS access can be carried out as appropriate to the expertise of the surgeon. VATS or minimally invasive surgery (including robotic-assisted approaches) should be strongly considered for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery. Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved. T3 (invasion) and T4 local extension tumours require en-bloc resection of the involved structure with negative margins. If a surgeon or centre is uncertain about potential complete resection, consider obtaining an additional surgical option from a high-volume specialised centre (National Comprehensive Cancer Network 2018).

6.1.3.5 Nodal assessment (during surgery)

The NCCN guidelines must be followed for margins evaluation and nodal assessment. N1 and N2 node resection and mapping should be a routine component of lung cancer resections. Accordingly, it is recommended that a minimum of 3 lobe-specific mediastinal nodal stations (N2), one of which should include station 7, and at least 1 N1 station—inclusive of the ones removed with the pulmonary specimen—have been sampled at the end of the procedure. Formal ipsilateral mediastinal lymph node dissection is recommended in general but is absolutely indicated for patients undergoing resection for N2 disease.

6.1.3.6 Margins

Margins slides including BM (bronchial), PA (pulmonary artery) and PV (pulmonary vein) are mandatory. Margin negative is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumour as R2 (NCCN NSCLC Guidelines 2020).

6.2 Preparation/handling/storage/accountability

No additional preparation or handling is required for osimertinib. For cisplatin, carboplatin and pemetrexed, refer to the Preparation and Handling instructions in accordance with the local label.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The investigational product label on the bottles specifies instruction of appropriate storage. The Investigator or designee (eg, unblinded pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Used/unused IP will be disposed of at non-Japan sites per local procedures and not returned to AstraZeneca for disposal.

For Japan: Study drugs will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the return of all unused IP to AstraZeneca. AstraZeneca will provide the study documents, "Procedures for Drug Accountability" and "Procedures for Drug Storage," which describe the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Patient enrolment and randomization

All patients will be centrally assigned to randomised study treatment using IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions and user guides for the IVRS, and/or the log-in information and directions for the IWRS will be provided to each site.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be re-used. Withdrawn patients will not be replaced.

Investigators should keep a record (ie, the patient screening log) of patients who entered pre-screening / screening.

At pre-screening / screening (D-28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures, or pulmonary function testing were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory procedures, imaging results and pulmonary function testing must have been obtained within 6 weeks prior to randomisation.
- Upon signing either the pre-screening or main study informed consent, patients will be identified to the IVRS/IWRS per country regulations. Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format PPD PPD This number is the patient's unique identifier and is used to identify the patient on the CRFs.
- Obtain tumour (mandatory where available) and plasma sample (mandatory) and send for centralised EGFR mutation status testing. Obtaining the tumour biopsy sample[2] should be given the highest priority if there is no pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx test result and, as such, the sample should be obtained and sent for central testing as soon as possible, which could be prior to the 28-day screening window (after obtaining signed informed consent) in order to permit analysis prior to randomisation. In the case that neither tumour tissue sample with preserved tumour tissue architecture, nor pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx EGFR test result per IFU from tumour sample is available, a tumour FFPE FNA sample collected per SoC prior to, or during, screening is acceptable for central EGFR mutation status confirmation using Idylla™ EGFR Mutation Test, when permitted by AstraZeneca. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment. Screening procedures may be obtained while EGFR mutation is being assessed (See Section 8.7.1.1).
- Record demographic data and other characteristics, including date of birth, age, sex, smoking history, and/or race/ethnicity (according to local regulations).
- Determine patient eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional). Patients who decide not to sign the specific genetic ICF, but the general study ICF, are eligible for study enrolment and all other study procedures.

Patients must not be randomised and treated unless all eligibility criteria have been met. If the patient is eligible (ie, all eligibility criteria have been met, including confirmation of EGFR mutation status):

[2] An archived tissue or new biopsy specimen, when no archived tissue is available, is acceptable. Patients will only undergo tumour biopsy if it is considered a medically acceptable risk by the investigator.

- Select the SoC treatment that the patient should receive prior to randomisation (based on the most appropriate option for the patient; the reason for this choice should be documented). This must be completed for all patients. The information will be recorded in the IVRS/IWRS system.
- Randomisation: Obtain a unique randomisation code via the IVRS/IWRS. Numbers will start at 001 and will be assigned PPD within each stratum by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 3 treatment groups.
- Initiate pre-treatments for chemotherapy, as described in the SoA (Table 1).
- Initiate study treatment(s) on Day 1.

If the patient is ineligible and not randomised, the IVRS/IWRS should be accessed to terminate the patient in the system.

6.3.2 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomised or started on study treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the patient.

6.3.3 Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomisation scheme in the IVRS/IWRS. The randomisation codes will be computer-generated by AstraZeneca R&D using the AstraZeneca Global Randomisation system AZRand and will be loaded into the IVRS/IWRS database. One randomisation list will be produced for each of the randomisation strata. A blocked randomisation will be generated, and randomisation will be balanced within the IVRS/IWRS at the central level.

Patients will be identified to the IVRS/IWRS per country regulations. Randomisation codes will be assigned PPD, within each stratum, as patients become eligible for randomisation. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomisation visit and subsequent treatment visits.

6.3.4 Methods for ensuring blinding

All patients will be centrally randomised using IVRS/IWRS.

For patients randomised to study Arms 1 and 2, the IVRS/IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit (pertaining to the double-blinded osimertinib/placebo study treatment component of each arm). Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre. The randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The Investigators choice of SoC chemotherapy in Arms 1 and 2 is single-blind, and therefore the Sponsor/Global Study Team are blinded to the specific SoC chemotherapy regimen to be taken by a patient.

Arm 3 is open-label for the personnel at study sites; however, the Sponsor/Global Study Team are blinded.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to any investigational product and that potentially require expedited reporting to regulatory authorities.

Personnel testing the pharmacokinetic samples will be unblinded to the investigational treatment for each patient.

6.3.5 Methods for unblinding

For patients randomised to study Arm 1 and 2, the IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest for the Investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual patient have been made and documented.

6.4 Treatment compliance

The administration of all study treatments, as well as any change from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations should be recorded in the eCRF. This information, plus drug accountability for all study treatments at every visit, will be used to assess compliance.

The study treatment(s) should be completely reconciled with supportive evidence provided in the source document, such as drug accountability log or equivalent documents.

The Investigational Product Storage Manager is responsible for managing study treatment from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

Osimertinib compliance will be calculated by the sponsor based on the drug accountability documented in the source document and eCRF by the site staff and monitored by the sponsor/designee (tablet counts). The objective is 100% compliance, and Investigators and the site staff should evaluate and review treatment compliance with the patient at each visit and take appropriate steps to optimize compliance.

6.5 Concomitant therapy

If medically feasible, patients taking regular medication (with the exception of strong inducers of CYP3A4) should be maintained on their regular medication throughout the study.

Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the main safety follow-up period (defined as either 28 days after the last dose of last study treatment for patient who do not undergo surgery, or 90-days post-surgery*).

* *For patients treated with adjuvant IP-osimertinib in the EFS follow-up period, the collection of concomitant medications should continue per the schedule in Table 2.*

Any concomitant treatment, procedure, medication, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrolment or receives during the study must be recorded in the source document and the applicable section of eCRF. along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded until the related AE is resolved, stabilised, is otherwise explained or patient is lost to follow-up.

Patients must be instructed not to take any medications in the neoadjuvant period, including over-the-counter products, without first consulting with the Investigator. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Restricted and prohibited concomitant medications

Prohibited, restricted, and permitted concomitant medications/therapies are described in Table 5 (prohibited medications), Table 6 (restricted medications), and Table 7 (permitted medications).

For questions related to specific medications, contact the Sponsor's Study Physician. Refer also to the guidelines for management of treatment-related toxicities in Section 8.5.5. Guidance on medications to avoid and those that require close monitoring (such as propofol), and washout periods is provided in Appendix G. For SoC chemotherapy agents, refer to the local prescribing information with regard to warnings, precautions, and contraindications.

Patients who have received prior treatment with immuno-oncology (IO) therapies should be closely monitored for an appropriate period of time after the last dose of the IO treatment, in accordance with the respective IO label, as immune-mediated adverse reactions with the IO therapy may occur at any time during or after discontinuation of therapy. The stop date of the prior IO drug therapy should be captured in the case report forms.

Table 5 Prohibited concomitant medications

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Must not be given while the patient is on study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Must not be given concomitantly while the patient is on study treatment. Note that concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
Live vaccines	Live vaccines should not be given while patient is receiving cisplatin, carboplatin and/or pemetrexed, and up to three months after the last dose of any of these therapies

Table 6 Restricted concomitant medications

Restricted medication/class of drug	Usage
Strong inducers of CYP3A4	Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be strong inducers of CYP3A4 whenever feasible. Such drugs must have been discontinued for an appropriate period before the patient enters screening and for a period of 3 weeks after the last dose of osimertinib/placebo. Patients may receive any medication that is clinically indicated for treatment of AEs.

Restricted medication/class of drug	Usage
Medications whose disposition is dependent upon the Breast Cancer Resistance Protein (BCRP) and/or P-glycoprotein (P-gp) with a narrow therapeutic index. See Appendix G for a list of drugs.	Closely monitor for signs of changed tolerability as a result of increased exposure to the concomitant medication while receiving osimertinib/placebo.
Rosuvastatin	Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.
Nonsteroidal Anti-Inflammatory Drugs	Patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates should not take these medications (other than an aspirin dose ≤1.3 grams per day) for 2 days prior, the day of, and 2 days after receiving pemetrexed. Patients taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) should not take these medications for 5 days prior, the day of, and 2 days after pemetrexed.
Warfarin or other anticoagulants	Due to the possibility of an interaction between oral anticoagulants and anti-cancer chemotherapy, there is requirement to monitor International Normalised Ratio (INR) frequently, if it is decided to treat the patient with oral anti-coagulants. Patients taking warfarin or other anticoagulant with pemetrexed should be monitored regularly for changes in prothrombin time or INR.
Colony stimulating factors (CSFs)	Granulocyte colony stimulating factors (G-CSF) should not be used prophylactically during Cycle 1. Following first cycle chemotherapy, growth factors may be used in accordance with the American Society of Clinical Oncology Clinical Practice Guideline Update on the use of WBC Growth factors (Smith et al 2015) or in accordance with local standards of care.
Antiemetic therapy	See Section 6.5.2
Drugs that prolong the QT interval	Detailed guidance is provided in Appendix G and additional specific guidance regarding anti-emetic drugs that can prolong the QT interval is provided in Section 6.5.2
Nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides, loop diuretics) therapies	Patients taking nephrotoxic and ototoxic therapies should not take these medications as these may potentiate cisplatin and carboplatin toxicities

Abbreviations: CYP3A4, Cytochrome P450 3A4.

Table 7 Allowed concomitant medications/therapies

Allowed medication/therapies/class of drug	Usage
Pre-medication will be allowed for patients enrolled in a chemotherapy-treatment arm.	To be administered as directed by the Investigator. This includes management of diarrhoea, nausea and vomiting. See Section 6.5.2 for further details on antiemetic therapy.
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" and/or "restricted", as listed above	Can be administered as prescribed by the Investigator.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management)	Can be administered as prescribed by the Investigator.
Calcium folinate/folinic acid	The use of calcium folinate/folinic acid in the management of pemetrexed overdose can be considered.
Leukocyte-depleted blood transfusions	Patients can have blood transfusions during study treatment. However, patients are not allowed to receive blood transfusions or platelet transfusions in order meet the inclusion criteria of the study (see inclusion criterion 8 in Section 5.1).
Corticosteroids	Please see Section 6.1.1.2 for details of corticosteroid pre-medication for patients receiving chemotherapy.

6.5.2 Antiemetic therapy

In principle, antiemetic premedication should be administered according to local standards of care. QTc interval prolongation has been observed in patients treated with osimertinib, however no QTc-related arrhythmias were reported in the FLAURA or AURA studies. Given that some antiemetic therapies have been associated with QT interval prolongation with or without Torsades de Pointes (TdP), caution is required with respect to co-administration of osimertinib/placebo with antiemetics in this study.

The Arizona Centre for Education and Research on Therapeutics (https://www.crediblemeds.org/) is a website that categorizes drugs based on the risk of causing QT prolongation or TdP. Information on these categories and antiemetic therapies is provided in Table 8. This list of drugs may not be exhaustive; moreover, the information regarding drugs in the table below is subject to change as new information becomes available. As such investigators should review the up-to-date website.

Table 8 QT/TdP risk category for antiemetic therapies

QT/TdP risk	Category Definition	Antiemetic therapies
Known risk of TdP	These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended.	Domperidone Droperidol Haloperidol Levomepromazine Levosulpiride Ondansetron
Possible risk of TdP	These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.	Dolasetron Granisetron Palonosetron Tropisetron
Conditional Risk of TdP	These drugs are associated with TdP BUT only under certain conditions of their use (eg, excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).	Metoclopramide

An additional risk category applies in relation to drugs to avoid in patients with Congenital Long QT Syndrome; however, these patients are not permitted to enrol in this study.

In the light of this information, the following guidance is given:

1. At screening patients are required to have serum electrolytes ≥LLN; ie, potassium, magnesium and calcium in the normal range. If during screening patients have electrolyte levels <LLN, measures can be taken to bring these into the normal range. During study treatment, electrolyte levels should be maintained in the normal range.
2. Investigators should review guidance that applies to all drugs (ie, not just anti-emetics) with the potential for interaction with osimertinib regarding QTc interval prolongation (see Appendix G).
3. In this study it is strongly recommended that antiemetic drugs from the known risk of TdP category are not administered, ie, ondansetron, domperidone, droperidol, haloperidol, levomepromazine, or levosulpiride. If it is considered essential to give a 5-HT3 receptor-antagonist, one of the following agents should be given if available: granisetron, dolasetron, tropisetron or palonosetron. However, as these drugs are categorized as having a possible risk of TdP, careful monitoring of ECGs and electrolytes is recommended. If it is essential to give a 5-HT3 receptor-antagonist and ondansetron is the only available 5-HT3 receptor-antagonist, careful monitoring with ECGs and electrolytes is recommended.

Note neurokinin-1 receptor antagonists such as aprepitant are not associated with QTc interval prolongation.

6.5.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

6.6 Dose modification

Dose modifications are permitted in the management of IP-related toxicities, as described in Section 8.5.5.

6.7 Treatment after the end of the study

After the EFS follow-up period, no further treatment will be provided to patients by AstraZeneca. Patients should be treated in accordance with local clinical practice guidelines (eg. NCCN guidelines).

7 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

7.1 Discontinuation of study treatment

Patients must be discontinued from all/any study treatment (osimertinib, cisplatin, carboplatin, and pemetrexed) if any of the situations listed below apply for that study treatment:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2)
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation defined in the guidelines for management of treatment-related toxicities (see Section 8.5.5), or as defined in the local prescribing information for the SoC agents
- Severe non-compliance with the Clinical Study Protocol (CSP), as judged by the Investigator or AstraZeneca (eg, refusal to adhere to scheduled visits)
- Pregnancy or intent to become pregnant
- Initiation of subsequent anticancer therapy, including another investigational agent

A patient continuing on at least 1 IP will not be considered discontinued from study treatment and will continue assessments per the SoA (Table 1 - Neoadjuvant period).

Patients randomised to receive osimertinib/placebo with SoC chemotherapy treatment can discontinue pemetrexed or platinum/pemetrexed and continue to receive osimertinib/placebo alone.

Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study.

7.1.1 Procedures for discontinuation of study treatment

The Investigator should instruct patients to contact the site before or at the time study treatment is stopped. A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs.

A treatment discontinuation visit should be performed as soon as a patient permanently discontinues all study treatment in the neoadjuvant period, and will include the assessments specified in the SoA (Table 1 - Neoadjuvant period: Discontinuation visit). For patients receiving AstraZeneca-supplied osimertinib in the EFS follow-up period of the study, a discontinuation visit should also be performed upon cessation of osimertinib treatment (Table 2 - EFS follow-up: Discontinuation visit).

The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF. The date of last intake of study treatment should also be documented in the eCRF, and all study treatment should be returned by the patient at the next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available SoC therapy, at the discretion of the Investigator.

Patients who have permanently discontinued study treatment will also need to be discontinued from the IVRS/IWRS.

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. The patient should continue attending subsequent study visits, per the SoA, and data collection should continue until the end of the study – see Section 7.1.1.1 and Section 7.1.1.2. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.1.1 Follow-up of patients' post-discontinuation of study treatment

All patients who discontinue study treatment in the neoadjuvant period will undergo a safety follow-up visit at 28-days (+14 days) after the last dose of the last administered study treatment. The assessments to be performed at this safety follow-up visit are detailed Table 1 (Safety follow-up visit).

For patients receiving AstraZeneca-supplied osimertinib in the EFS follow-up period of the study, a safety follow-up visit at 28-days (+14 days) after the last dose of osimertinib should also be performed (Table 2 - EFS follow-up period: Safety follow-up visit).

7.1.1.2 Follow-up for survival

Patients who fail to undergo surgery due to disease progression, fail to achieve complete resection at surgery, or have an EFS event in the EFS follow-up period will be followed up for survival status as indicated in Table 2 (Survival period) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician.

7.2 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow-up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent for:

- All further participation in the study including any further follow-up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Appendix C)

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely. AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) during survival follow-up from publicly available sources, in accordance

with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

7.3 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the patient's status at that time.

Patients who decline to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up."

Investigators should document attempts to re-establish contact with missing patients throughout the study period. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by, eg, repeat telephone calls, certified letter to the patient's last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study, the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support secondary endpoints of EFS, DFS, and OS analyses, the survival status of all patients in the full analysis and the safety analysis set should be re-checked, which includes those patients who withdrew consent or are classified as "lost to follow-up.":

- Potentially lost to follow-up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable eCRF modules will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable eCRF modules will be updated.)

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1 and Table 2).

The Investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria (see Section 5.1 and Section 5.2). The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable (see Section 5.4).

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).

8.1 Efficacy assessments

This study will evaluate the primary endpoint of MPR in the Full Analysis Set (FAS). Efficacy assessments of pCR, downstaging, EFS, DFS, and OS in the FAS will also be investigated (see Section 9.4.1 for the definitions of each of these endpoints).

8.1.1 Surgical specimen assessments

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), ideally within 8 weeks after surgery. 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 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).

8.1.2 Tumour imaging assessments

8.1.2.1 Contrast-enhanced CT scan

Radiological tumour assessment from scans of the chest and abdomen (including the entire liver and both adrenal glands) using images obtained via CT (or MRI) with IV contrast, will be performed according to image acquisition guidelines provided by the Contract Research Organisation (CRO). If patients are contraindicated to CT contrast agents, a contrast-enhanced MRI or non-contrast CT will be acceptable (contrast-enhanced MRI preferred over non-contrast CT).

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. In those patients who are contraindicated to contrast agents based on gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), a non-contrast MRI would be sufficient. In those patients with a contraindication to MRI, a (contrast-enhanced) CT of the brain would be sufficient. Further details of the recommended CT and MRI acquisition parameters will be documented in a separate image acquisition guidelines document.

The same imaging modality used for the baseline tumour assessment should be used for each subsequent follow-up assessment throughout the study, unless contraindicated.

A baseline scan should be collected during the screening period (D-28 to D-1; see Table 1 – Screening period) for disease staging and for use as a baseline for the post-neoadjuvant treatment/pre-surgery scan. This baseline scan should ideally be performed as close as possible to the start of study treatment. Scans obtained per the patient's SoC prior to randomisation do not need to be repeated and are acceptable to use as baseline evaluations, if the following criteria are met:

- The scan was obtained within 6 weeks of randomisation
- The scan is performed using the method requirements outlined above (contrast enhanced CT is recommended for imaging the chest and abdomen, including liver and adrenal glands, whereas contrast-enhanced MRI is recommended for brain scans)
- The same technique/modality can be used throughout the trial for a given patient; and

- Appropriate documentation indicating that these radiographic tumour assessments were performed as standard of care is available in the patient's source notes.

Patients with a CT scan of the brain obtained per the patient's SoC prior to randomisation will not be required to have an MRI brain scan during screening if the criteria above 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 Table 1 – Surgery period).

EFS follow-up period tumour assessments are then to occur according to the schedule outlined in Table 2 (EFS follow-up period). 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 adjuvant 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 recurrence, 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 recurrence, withdrawal of consent, death, or until approximately 5.5 years after the last patient is randomised (whichever occurs first). Such patients will be determined to have an EFS event when the investigator identifies progression that precludes surgery 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 progression, careful consideration should be given to the extent of imaging coverage at 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 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 (see Section 8.4.10). 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 (see Section 9.4.1.3) or DFS event (see Section 9.4.1.5).

8.1.2.2 Whole-body PET scan

PET and CT hybrid imaging (PET–CT) with ^{18}FDG is widely being used in oncology for diagnosis, staging, restaging and therapy response evaluation due to its ability to measure metabolic changes (Kandathil et al 2018).

In the present study, 2 whole-body (base of skull to mid-thigh) ^{18}FDG-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; Wahl et al 2009, Hyun et al 2016) by Blinded Independent Central Review and to explore PET-CT radiomics signatures and to assist with TNM (re)staging according to the investigator's judgement.

Dedicated CT scanners are preferred for diagnostic CT imaging. However, hybrid PET/CT scanners may be used to acquire the required diagnostic CT images if the CT produced by the scanner is of diagnostic quality (using adequate contrast) and if it adheres to the

specified scan parameters in the CT section of the image acquisition guidelines. The contrast enhanced diagnostic CT scan should be performed after the PET scan.

The image acquisition guidelines describe in detail the methods for controlling the quality of FDG-PET imaging conditions to ensure the comparability of PET images from different time points and between multiple sites. Recommendations for subject preparation and scanning procedures (eg, duration of fast, blood glucose level, intravenously injected ^{18}FDG dose, injection-to-imaging time) can be found in the image acquisition guidelines. Methods must remain consistent between the 2 scans to allow quantitative expression of the changes in PET measurements and assessment of the overall response with PERCIST. Quantification of FDG uptake and assessment with PERCIST will be performed centrally by an appointed CRO.

8.1.2.3 Central collection of scans

All images, including unscheduled visit scans and scans from patients that did not undergo surgery, will be collected on an ongoing basis and sent to an AstraZeneca-appointed CRO for QC and storage for blinded independent central reads, 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. 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.

8.1.3 Overall survival (OS) assessments

Assessments for survival should be conducted every 3 months, (see Table 2 – Survival period) for patients not achieving surgery due to disease progression in the neoadjuvant period, or following an EFS event in the EFS follow-up period.

Survival information may be obtained via telephone contact with the patient, patient's family, by contact with the patient's current physician, or local death registries as described in Section 7.2.

Details of first and subsequent therapies for cancer (including radiotherapy) will be collected. In addition, patients in survival follow-up will be contacted following the DCO for the EFS analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO.

8.2 Clinical outcome assessments

A clinical outcome assessment (COA) is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. COAs can be reported by a patient (PRO), a clinician (ClinRO), an observer (ObsRO), or through a performance-based assessment (FDA-NIH BEST Resource).

A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on symptoms, function, and other health-related quality of life (HRQoL) of the patient to aid understanding of the risk-benefit profile.

A PRO is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important in evaluating the effectiveness of study treatments in clinical studies and will aid in understanding of the benefit/risk evaluation Kluetz et al 2018).

The following PRO instruments will be administered in this study (see Appendix F):

- EORTC QLQ-C30 v3 (core questionnaire) (see Section 8.2.1)
- EORTC QLQ-LC13 (lung cancer-specific module) (see Section 8.2.2)
- EQ-5D-5L (see Section 8.2.3)

PROs will be administered and translated into the language of the country according to the schedule described in the SoA (Table 1 and Table 2).

8.2.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures symptoms, functioning, and global health status/quality-of-life (GHS/QoL; Aaronson et al 1993) for all cancer types.

Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item GHS/QoL scale, 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea), and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population (see Appendix F).

8.2.2 EORTC QLQ-LC13

The EORTC QLQ-LC13 questionnaire is a well-validated complementary module measuring lung cancer-associated symptoms and side effects from conventional chemotherapy and radiotherapy (Bergman et al 1994).

The EORTC QLQ-LC13 includes questions assessing cough, haemoptysis, dyspnoea, site-specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy, alopecia (treatment-related side effects), and pain medication (see Appendix F).

8.2.3 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (EuroQol 2015). The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Respondents also assess their health today using the EQ-VAS (visual analogue scale), which ranges from 0 (worst imaginable health) to 100 (best imaginable health; see Appendix F).

8.2.4 Administration of PRO questionnaires

Patients will perform the PRO assessments using an electronic tablet (ePRO) during clinic visits at the time points indicated in the SoA (Table 1 and Table 2). A web backup solution will be in place if technical problems with the tablet.

Each site must allocate the responsibility for the administration of the ePRO devices to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent.

Approximately 10 to 20 minutes is required for patients to complete the questionnaires.

The below instructions should be followed when collecting ePRO data:

- PRO questionnaires must be completed prior to any other study procedures or discussions (following informed consent), including medication treatments, and before discussion of disease progression to avoid biasing the patient's responses to the questions.
- PRO questionnaires should be completed by the patient in a quiet and private location.
- The patient should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should explain to patients the value and relevance of these data so they are motivated to comply with questionnaire completion.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the patient has any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor.
- All questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items.

- The patient must not receive help from relatives, friends, or clinic staff to answer the ePRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the patient will be exempted from completing the ePROs at that clinic visit.
- Site staff must not read or complete the ePRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient is exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.
- Site staff must administer questionnaires available in the language that the patient speaks and understands. Questions must not be read in an available language and translated into another language for the patient.
- It is vital that the ePRO reporting is initiated before dosing on C1D1, as specified in the SoA, to capture the effect of study treatment

A key aspect of study success is to have high PRO compliance. Therefore, it is essential to follow the SoA, and that sites make sure the device is charged and fully functional at all times in order to minimize missing data. Site staff will document in source documents and in eCRF the reason why a patient could not report assessments on a visit.

8.3 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.3.1 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.

8.3.2 Clinical safety laboratory assessments

Blood samples for the determination of clinical chemistry and haematology are to be taken at the times indicated in the SoA (Table 1), and as clinically indicated. The protocol-required laboratory assessments to be measured at each timepoint are defined in Table 9 (clinical chemistry) and Table 10 (haematology); and must be conducted in accordance with local practice.

Urine sample collection for urinalysis (see Table 11) is to be performed at screening and subsequently as clinically indicated.

Table 9 Clinical chemistry (serum or plasma)

Albumin	Creatinine clearance [b]
Alkaline phosphatase (ALP) [a]	Cystatin C [e]
Alanine transaminase (ALT) [a]	Glucose
Aspartate transaminase (AST) [a]	Lactate dehydrogenase (LDH) [c]
Bilirubin, total [a]	Magnesium
Blood creatinine	Potassium
Calcium, total	Sodium
Blood creatine phosphokinase [e]	Urea or blood urea nitrogen [d]

[a] 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.

[b] Creatinine clearance will be calculated by the Investigator using Cockcroft-Gault (refer to Appendix H) or assessed by 24-hour urine creatinine.

[c] LDH is an additional variable collected during screening only

[d] Depending on local practice.

[e] CPK and cystatin C are required in patients randomised after local approval of CSP v3.

Table 10 Haematology (whole blood)

Haemoglobin (Hb)	Leukocyte differential count (absolute count) [a]
Red Blood Cell (RBC) count	Neutrophils
Haematocrit	Lymphocytes
Reticulocytes	Monocytes
Platelet count	Basophils
Leukocyte count	Eosinophils

a The value is to be provided as percentage of the leukocyte count if the absolute leukocyte differential counts are not available.

Table 11 Urinalysis (dipstick)

Blood	Glucose
Protein	

Note: Urinalysis should be done at baseline (screening), Day 1 of adjuvant treatment, and as clinically indicated.

Clinical chemistry and haematology assessments that have been performed during screening and within 14 days prior to starting study treatment do not have to be repeated on C1D1 providing that the patient's clinical condition has not changed. All laboratory assessments occurring on study visit days are to be conducted prior to receiving study treatment, unless otherwise indicated. Results for full blood count, liver function tests, electrolytes, and creatinine clearance (calculated from the Cockcroft-Gault equation or measured from a 24-hour urine creatinine test) must be available before commencing study treatment on the first day of each neoadjuvant treatment cycle (C1D1, C2D1, and C3D1;

within 3 days) and reviewed by the treating physician or Investigator prior to dosing. These tests subsequently do not need to be repeated on the day of study treatment administration, unless clinically indicated.

Clinical laboratory safety tests will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. The laboratory results are to be signed and dated and retained at centre as source data for laboratory variables.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded in the appropriate eCRF.

Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours) and recorded in the eCRF. For information on how AEs based on laboratory tests are to be recorded and reported, see Section 8.4.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.3.3 Pregnancy testing

Women of childbearing potential are required to have a pregnancy test within 14 days prior to the first dose of study treatment, and then Q3W prior to study treatment administration on the first day of each treatment cycle in the neoadjuvant period of the study. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to receiving any study treatment.

For women of childbearing potential receiving AstraZeneca-supplied osimertinib in the EFS follow-up period of the study, pregnancy testing (blood or urine tests are acceptable based on the site's standard clinical practice) should be performed prior to osimertinib dispensing at each visit.

8.3.4 Physical examinations

A complete physical examination is to be performed and documented in the eCRF at screening, the pre-surgical assessment visit, all EFS follow up visits, and during the IP discontinuation visit (if applicable) (see Table 1 and Table 2). Height will be measured during screening only.

A complete physical examination is to include an assessment of head and neck (including ears, eyes, nose and throat), and the respiratory, cardiovascular, gastrointestinal, haematological/lymphatic, endocrine, musculoskeletal and neurological systems.

In addition, targeted physical examinations should be carried out by the Investigator on the basis of clinical observations and symptomatology at any time, if clinically indicated.

Investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as AEs; see Section 8.4.7 for details.

8.3.5 Vital signs and body weight

Vital signs and body weight are to be taken at the times indicated in the SoA (Table 1), and as clinically indicated.

Vital signs (to be taken before blood collection for laboratory tests) will consist of temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). If blood pressure is outside a normal clinical range, then 2 additional readings should be taken and the average of the 3 readings (recorded at intervals of at least 1 minute) will be recorded on the CRF. Blood pressure and pulse measurements will be assessed in a supine position (or sitting, if supine is not feasible) with a completely automated device. Manual techniques will be used only if an automated device is not available.

Situations in which vital signs results should be reported as AEs are described in Section 8.4.7. For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.3.6 Electrocardiograms

Resting 12-lead ECGs will be performed at screening and at the pre-surgical assessment visit, and if clinically indicated (eg, in the event of a cardiac AE) (see Table 1).

For patients receiving AstraZeneca-supplied osimertinib in the EFS follow-up period of the study, ECGs should be performed if clinically indicated (Table 2).

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 5 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study, if possible.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist, if appropriate. The paper copies should be filed in the patient's medical records as source documents.

Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

If the Investigator considers an abnormal ECG finding at screening or baseline to be clinically significant, that finding should be reported as a concurrent condition. For all ECGs, details of rhythm, ECG intervals and an overall evaluation will be recorded.

Situations in which ECG results should be reported as AEs are described in Section 8.4.7. Any clinically significant abnormal ECG finding during the treatment period should be recorded in the source document and the AE section of eCRF, according to standard AE collection and reporting processes. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

Patients experiencing a QTc greater than 500 msec on at least 2 separate ECGs must have osimertinib treatment interrupted until the QTc interval is less than 481 msec, or recovery to baseline if baseline QTc is greater than or equal to 481 msec.

Patients experiencing QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart osimertinib treatment.

8.3.7 Echocardiogram/MUGA scan

An echocardiogram (ECHO) or MUGA scan to assess left ventricular ejection fraction (LVEF) will be performed during the screening period, during the pre-surgical assessment visit, and if clinically indicated (eg, in the event of a cardiac AE).

For patients receiving AstraZeneca-supplied osimertinib in the EFS follow-up period of the study, LVEF assessment and MUGA cardiac monitoring must be performed at the first EFS follow-up visit, and the Week 12 and Week 24 EFS follow-up visits.

The modality of the cardiac function assessments must be consistent within a patient (ie, if ECHO is used for the screening assessment, then ECHO should also be used for subsequent scans). Patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken.

If a patient has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

Situations in which ECHO or MUGA scan results should be reported as AEs are described in Section 8.4.7.

8.3.8 ECOG performance status

ECOG PS will be assessed during screening and at the times specified in Table 1.

Performance status assessment will be based on the following scale:

0 Fully active; able to carry out all usual activities without restrictions

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or 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; unable to carry out any self-care and totally confined to bed or chair

5 Dead

Any significant change from baseline or screening must be reported as an AE.

8.3.9 Brain MRI/CT

A brain MRI (preferred) or CT will be performed at screening and at disease recurrence. (see Section 8.1.2.1 for further details).

8.4 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.4.3.

8.4.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.2 Time period and frequency for collecting AE and SAE information

During pre-screening, AEs (including SAEs) relating to study procedures will be collected from the time of signature of the Prescreening ICF until the patient is screen failed, or signature of the Screening ICF. All AEs (including SAEs) will be collected for all patients from the time of signature of the Screening ICF for the study until the main safety follow-up period is completed (defined as either 28 days after the last dose of last study treatment for patients who do not undergo surgery, or 90 days post-surgery), as shown in Table 12. Any AE with an onset date after the completion of the safety follow-up period (as defined above), that is considered to be possibly related to one or 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 period (non-IPs) 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 adverse events of special interest (AESIs; see Section 8.4.12) will be collected at the first EFS follow-up 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 osimertinib).

The time period for AE and SAE collection is outlined in Table 12.

Table 12 Time period and collection of AEs and SAEs

Prescreening (signing of Prescreening ICF until screen failure or signing Screening ICF)	Screening period (signing of ICF to C1D1)	Neoadjuvant period (including surgery and safety follow-up) [a]	Adjuvant osimertinib treatment in the EFS follow-up period (including safety follow-up) [b]	Survival follow-up (after completion of the safety follow-up periods)
All SAEs and AEs related to study procedures	All AEs, SAEs, and AESIs	All AEs, SAEs, and AESIs	SAEs and AESIs [c, d]	SAEs and AESIs, if related to prior study treatment [e]

[a] Commences from C1DI until 90 days post-surgery for patients undergoing surgery or until 28 days after the last dose of neoadjuvant IP for patients who did not undergo surgery. Any AE with an onset date after the completion of the safety follow-up period (as defined above in the text), that is considered to be possibly related to one or more study drugs (or study procedures) should be reported as an AE or SAE, as applicable.

[b] Only applicable to patients receiving AstraZeneca-supplied osimertinib as an IP in the EFS follow-up period. SAEs assessed as possibly related to optimal care medication in the EFS follow-up period (non-IPs) should be reported via local pharmacovigilance procedures.

[c] To be collected at the first EFS follow-up visit, the Week 12 post-surgery visit, the Week 24 post-surgery visit, and subsequently every 12 weeks (±14 days); at treatment discontinuation, and at safety follow-up (28 days after the last dose of osimertinib).

[d] In case of osimertinib continuation or rechallenge during/after Grade 1 or 2 ILD, collect all AEs (not only SAEs and AESIs). See section 8.5.6.4.1.

[e] Additional safety assessments may be performed as per local clinical practice, but will not be collected as part of study data capture. AstraZeneca will collect information on SAEs, AESIs, and pregnancy (within 6 weeks of last dose) via telephone if the EDC system is not available (see Section 8.5).

All SAEs occurring in the AE collection period will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

In accordance ICH guidelines, AEs that are emergent during the EFS follow-up period of the study (when patients are receiving non-investigational products as per investigators' choice) will be reported in accordance with local pharmacovigilance processes.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. Any new or unresolved AE observed at the patient's last AE assessment visit (28-day Safety follow-up visit for patients not undergoing surgery, or 90 days for patients undergoing surgery) should be followed until the event resolves, stabilises, is otherwise explained, or the patient is lost to follow-up.

8.4.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The start and stop date of the AE
- The maximum CTCAE grade (with the exception of AEs of ILD/pneumonitis, for which all CTCAE grade changes should be recorded in the eCRF; see Section 8.5.6.4.1 for further details)
- Whether the AE is serious (Appendix B)
- Investigator causality assessment against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused patient's withdrawal from study (yes or no)
- Administration of treatment for the AE
- Outcome of the AE

In addition, the following variables will be collected for SAEs:

- Date AE met SAE criteria

- Date Investigator became aware of SAE
- Seriousness criteria
- Date of hospitalization (if applicable)
- Date of hospital discharge (if applicable)
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Whether an autopsy was performed (if applicable)
- Causality assessment in relation to study procedure(s) (yes or no)
- Causality assessment to other medication(s) (yes or no)
- Description of the SAE

The grading scales found in the NCI CTCAE Version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE Version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.4.5 Causality collection

The Investigator will assess causal relationship between Investigational Product and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs, causal relationship to other medication(s) and study procedures will also be assessed. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B.

8.4.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: "Have you/the patient had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom is to be recorded separately.

8.4.7 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests, vital signs, ECGs, and ECHO/MUGA scans will be summarised in the Clinical Study Report (CSR). Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs, ECGs, or ECHO/ MUGA scans are therefore only to be reported as AEs if they fulfil any of the SAE criteria, are the reason for dose modification, interruption, or discontinuation of treatment with the IP, are the reason for delay of surgery or require treatment or non-planned visits.

If deterioration in a laboratory value, vital sign, ECG, or ECHO/MUGA scan is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (eg, 'anaemia' rather than 'low haemoglobin'). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Sections 8.4.8 and 8.4.9.

8.4.8 Disease under study

Symptoms of the disease under study are those which might be expected to occur as a direct result of the underlying NSCLC. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

8.4.9 Disease progression/recurrence

Disease progression/recurrence can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new lesions should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.4.10 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.4.11 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be documented in the CRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the CRF. The report should contain a comment regarding the co-involvement of progressive disease, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the CRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study treatment should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.4.12 Adverse events of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding the safety profile of osimertinib and require close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the CRF. Serious AESIs will be recorded and reported as per Section 8.5.1.

The AESIs for the study are:

- **Interstitial lung disease (ILD), including pneumonitis:** ILD and pneumonitis are adverse drug reactions for osimertinib. The topic is an AESI for this study in order that data representing a change to the established profile of this important identified risk is captured for full characterisation. The standard AE reporting processes for AEs (as described in Section 8.4) remains unchanged. Details of the standard monitoring and management guidelines of ILD are located in Section 8.5.6.4.1.
- **Cardiac failure:** Cardiac failure is not an adverse drug reaction for osimertinib. However, the topic is categorised as an important potential risk, based on changes in cardiac contractility observed in patients during the clinical development programme for osimertinib. Thus, the topic is an AESI for this study in order that data representing

evidence of a possible causal role of the study drugs in this population is captured for full characterisation. The standard AE reporting processes for relevant AEs (as described in Section 8.4) remains unchanged. Details of the standard monitoring and management guidelines of cardiac failure are located in Section 8.5.6.4.6.

8.5 Safety reporting and medical management

8.5.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for osimertinib and the local label for SoC chemotherapy.

8.5.2 Pregnancy

All pregnancies and outcomes of pregnancy that occur during the course of the study and within 6 weeks of the last dose of osimertinib/placebo, including pregnancy in the partner of male patients, should be reported to AstraZeneca.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, all study treatment(s) should be discontinued immediately.

Pregnancy itself is not regarded as an AE, unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the neoadjuvant period of the study or within 6 weeks of the final dose of osimertinib/placebo, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.5.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.5.2.2 Paternal exposure

Male patients must use barrier contraceptives (ie condoms) during sex with a female partner of child-bearing potential (including a pregnant partner) from the start of dosing until at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib. In addition, patients must refrain from donating sperm from the start of dosing until at least 6 months after discontinuing chemotherapy or at least 4 months after discontinuing osimertinib.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) occurring from the date of the first dose of study treatment until 4 months after the last dose of study treatment should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

8.5.3 Overdose

Investigators are advised that any patient who receives a higher dose of any study treatment than intended should be monitored closely for signs of toxicity, managed with appropriate supportive care if clinically indicated, and followed up prospectively.

8.5.3.1 Osimertinib (or placebo)

Use of osimertinib (or placebo) in doses in excess of that specified in the protocol (ie, 80 mg within a 24-hour period) is considered to be an overdose.

A maximum tolerated dose has not been established for osimertinib, and there is no specific treatment in the event of osimertinib overdose. In case of suspected overdose, osimertinib should be withheld and symptomatic treatment initiated.

If an overdose on an AstraZeneca study treatment occurs during the neoadjuvant study period, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site. For overdoses associated with a SAE, the standard reporting timelines apply; see Section 8.4.2. For other overdoses, reporting must occur within 30 days.

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

8.5.3.2 Standard of care

For SoC chemotherapy, refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, please record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.5.4 Medication error, drug abuse and drug misuse

8.5.4.1 Timelines

If an event of medication error, drug abuse **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an

SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.5.1) and **within 30 days** for all other events.

8.5.4.2 Medication error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an investigational medicinal product (IMP)/study intervention or AstraZeneca non-IMP (NIMP) that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of Medication Error can be found in Appendix B 4.

8.5.4.3 Drug abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP/study intervention or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.5.4.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study intervention(s) or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of Drug Misuse can be found in Appendix B 4.

8.5.5 Reporting of overdose

An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP/study intervention or AstraZeneca NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.5.1) and **within 30 days** for all other overdoses.

For participants receiving SoC chemotherapy, if any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.5.6 Management of study treatment-related toxicities

8.5.6.1 General dose adjustments for adverse events

If appropriate, the Investigator may attribute each toxicity event to cisplatin/carboplatin, pemetrexed or osimertinib/placebo alone or to a combination of study treatments and use a stepwise dose modification according to Table 13, Table 14, Table 15, and Table 16. Dose modification can be implemented for 1, 2 or 3 of the study treatment components depending upon the Investigator's assessment of causality. If, in the opinion of the Investigator, a toxicity is considered to be due predominantly to 1 component of the study treatment (platinum agent, pemetrexed or osimertinib/placebo) and the dose of that component is delayed or modified in accordance with the guidelines below, the other components may be administered if there is no contraindication. If a patient experiences several toxicities and there are conflicting recommendations for those toxicities, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Dose modifications for toxicities must be based on the maximum toxicity experienced during a treatment cycle. Toxicity must resolve to CTCAE Grade ≤1 or baseline prior to resumption of study treatment (see Section 8.5.6.2 and Section 8.5.6.3 for exceptions).

There is a maximum of 2 dose reductions for each component of chemotherapy treatment (ie, cisplatin, carboplatin or pemetrexed). If a patient experiences a toxicity that would cause a third dose reduction for any component of chemotherapy, that agent must be discontinued. Only 1 dose reduction is permitted for osimertinib/placebo treatment. If a patient experiences a toxicity associated with osimertinib/placebo that would cause a second dose reduction, osimertinib/placebo must be discontinued. If a dose reduction for toxicity occurs with any agent, the dose of that agent may not be re-escalated.

Patients receiving pemetrexed/cisplatin or pemetrexed/carboplatin with osimertinib who discontinue cisplatin alone or carboplatin alone may, at the Investigator's discretion, be switched to the alternative platinum agent with pemetrexed for the remainder of the platinum doublet cycles. Patients receiving pemetrexed/cisplatin or pemetrexed/carboplatin, with osimertinib/placebo who discontinue cisplatin or carboplatin can continue to receive pemetrexed with osimertinib/placebo if considered appropriate. Patients who discontinue platinum/pemetrexed can continue to receive osimertinib/placebo alone if considered appropriate. Similarly, patients may discontinue osimertinib/placebo and continue on chemotherapy alone if appropriate. Chemotherapy may be interrupted for a maximum of 3 weeks (ie, 6 weeks since the last dose of chemotherapy); osimertinib/placebo may be interrupted for a maximum of 3 weeks (with the exception of adjuvant osimertinib interruption for Grade 1 or 2 ILD/pneumonitis, as noted in Section 8.5.6.4.1). Patients withdrawn from all treatment because of toxicity should be observed until resolution of the toxicity.

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes are to be documented in the patient's chart and recorded on the eCRF.

Table 13 Dose Modifications for Study Treatments

	Initial dose	Dose reduction 1	Dose reduction 2	Dose reduction 3
Cisplatin	75 mg/m^2	56 mg/m^2	38 mg/m^2	Discontinue
Carboplatin	AUC5 Maximum dose 750 mg	AUC3.75 Maximum dose 562.5 mg	AUC2.5 Maximum dose 375 mg	Discontinue
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue
Osimertinib	80 mg/placebo once a day	40 mg/placebo once a day	Discontinue	Not applicable

8.5.6.2 Dose adjustment information for osimertinib

If a patient experiences a CTCAE Grade 3 or higher or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, not covered by the specific guidance below, where the investigator feels that there is a reasonable possibility of a causal relationship with osimertinib/placebo, dosing of osimertinib/placebo will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity does not resolve or revert to ≤CTCAE Grade 2 within 3 weeks of withholding osimertinib/placebo, osimertinib/placebo must be permanently discontinued and the patient should be observed until resolution of the toxicity. If the toxicity resolves or reverts to ≤CTCAE Grade 2 within 3 weeks of withholding osimertinib/placebo, treatment with osimertinib/placebo may be restarted at the same dose, 80 mg QD/placebo or a lower dose (osimertinib 40 mg QD/placebo), with discussion and agreement with the AstraZeneca Study Team Physician as needed. Following restart of treatment, the patient should be closely monitored for recurrence. Further guidance is provided in Table 14 and text below.

Table 14 Dose adjustment information for adverse reactions

Adverse reaction [a]	Dose modification
ILD/Pneumonitis	If ILD/Pneumonitis occurs in the neoadjuvant period, osimertinib must be permanently discontinued. If ILD/Pneumonitis occurs during treatment with adjuvant osimertinib, please see Section 8.5.6.4.1 for additional information, including ILD/pneumonitis dose modification and toxicity management.
QT interval >500 msec on at least 2 separate ECGs	Withhold osimertinib/placebo until QTc interval is <481 msec, or recovery to baseline if baseline QTc is >481 msec, within 3 weeks of interruption, then restart at reduced dose (40 mg QD/placebo) or at 80 mg (at the discretion of the investigator, to allow for situations where causality in relation to osimertinib may be difficult to determine).
QT interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib/placebo
Stevens Johnson Syndrome; Toxic epidermal necrolysis	Permanently discontinue osimertinib
Aplastic anaemia	Permanently discontinue osimertinib

Adverse reaction [a]	Dose modification
Grade 3 or higher non-hematological adverse reaction causally related to osimertinib/placebo	Withhold osimertinib/placebo for up to 3 weeks
Grade 4 hematological laboratory value or grade 3 hematological laboratory value with clinical sequelae, regardless of causality, specific parameters are listed below – see Section 8.5.6.4.7	Withhold osimertinib/placebo for up to 3 weeks

[a] The intensity of the clinical adverse events graded by CTCAE version 5.0.

8.5.6.3 Dose adjustment information for chemotherapy

If a patient experiences a CTCAE Grade 3 or higher or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation where the investigator feels that there is a reasonable possibility of a causal relationship with chemotherapy, dosing of chemotherapy should be delayed and supportive therapy administered as required in accordance with local practice/guidelines. If such toxicity does not have a reasonable possibility of a causal relationship with osimertinib/placebo per Investigator assessment, osimertinib/placebo can be continued at the tolerated dose.

If the toxicity to chemotherapy resolves or reverts to ≤CTCAE Grade 1 (platelet count ≥100 x 10^9/L) within 3 weeks of onset, treatment with chemotherapy may be restarted at the same dose, or at a reduced dose in accordance with Table 15 and Table 16, with discussion and agreement with the AstraZeneca Study Team Physician as needed. Dose adjustments for haematological toxicity should be based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Following restart of treatment, the patient should be closely monitored for recurrence. Further guidance is provided in Table 13 and in the text below.

Dosing must be delayed for any of the following on Day 1 of each cycle:

- Absolute neutrophil count (ANC) <1.5 x 10^9/L
- Platelets <100 x 10^9/L
- Creatinine clearance <45 mL/min
- ≥Grade 2 AST, ALT or bilirubin
- Any ≥ Grade 3 drug-related AE
- Any AE that in the opinion of the Investigator, would preclude administration of the next cycle of chemotherapy

Patients requiring a dose delay for chemotherapy should be reviewed weekly or more frequently until all criteria for resumption of chemotherapy are met. If treatment interruption due to toxicity is >3 weeks (ie, 6 weeks since the last dose of chemotherapy), chemotherapy must be permanently discontinued.

Chemotherapy can be resumed when all of the following criteria are met:

- ANC ≥1.5 x 10^9/L

- Platelets ≥100 x 10^9/L
- Creatinine clearance ≥45 ml/min
- Resolution of ≥Grade 2 AST, ALT or bilirubin to ≤Grade 1
- Resolution of ≥Grade 3 drug-related AEs to ≤Grade 1 or baseline (chemotherapy can be given in the presence of Grade 2 alopecia and fatigue)

In the event that a dose of chemotherapy is delayed due to toxicity, the next dose should be given as soon as possible according to Section 8.5.6.1. If treatment cycles are adjusted due to toxicity, all procedures, will be completed relative to the adjusted cycle and not weeks on treatment. All 3 cycles of chemotherapy should be given if clinically appropriate.

Specific dose modification advice is provided in Table 15 and Table 16. The recommended dose modifications serve as a guide and do not replace Investigator judgment and applicable local label recommendations, if more stringent.

Table 15 Recommended dose modifications for chemotherapy-associated haematological toxicity (based on nadir counts)

Haematological toxicity	Pemetrexed	Cisplatin	Carboplatin
Platelet counts ≥50 x 10^9/L **and** ANC ≥ 0.5 x 10^9/L	500 mg/m^2	75 mg/m^2	AUC5 Maximum dose 750 mg
Platelet counts ≥50 x 10^9/L **and** ANC <0.5 x 10^9/L	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Platelet counts ≤50 x 10^9/L without bleeding **and** any ANC result	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Any platelets **and** febrile neutropenia[a] (CTCAEv5)	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Platelet counts ≤50 x 10^9/L with ≥CTCAE Grade 2 bleeding **and** any ANC result	250 mg/m^2	38 mg/m^2	AUC 2.5 Maximum dose 375 mg

[a] Febrile neutropenia defined as ANC <1 x 10^9/L and single temperature of >38.3º degrees (101º Fahrenheit) or a sustained temperature of ≥38º (100.4º Fahrenheit) for more than one hour

Table 16 Recommended dose modifications for chemotherapy-associated non-haematological toxicity

Adverse event	CTCAE Grade [a]	Pemetrexed	Cisplatin	Carboplatin
Diarrhoea	Any episode requiring hospitalisation (irrespective of grade) or Grade 3 or 4	375 mg/m^2	56 mg/m^2	AUC5 Maximum dose 750 mg
Mucositis	Grade 3 or 4	250 mg/m^2	75 mg/m^2	AUC5 Maximum dose 750 mg
Neurotoxicity	Grade 2	500 mg/m^2	38 mg/m^2	AUC5 Maximum dose 750 mg
	Grade 3 or 4	Discontinue	Discontinue	Discontinue

Table 16 Recommended dose modifications for chemotherapy-associated non-haematological toxicity

Adverse event	CTCAE Grade [a]	Pemetrexed	Cisplatin	Carboplatin
Interstitial lung disease/pneumonitis	Any Grade	Discontinue	Discontinue	Discontinue
Other non-haematological toxicity [b]	Grade 3 or 4	375 mg/m^2	56 mg/m^2	AUC 3.75 Maximum dose 562.5 mg

[a] CTCAE version 5.0.

[b] Except for transient fatigue, transient arthralgia/myalgia or other events judged by the Investigator as not requiring dose modification.

8.5.6.4 Information on Specific Adverse Events

8.5.6.4.1 ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD/pneumonitis is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters, etc) will be captured in the eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered. Re-administration of osimertinib following episodes of ILD in osimertinib-treated patients participating in a Japanese postmarketing surveillance study is described in Gemma et al 2020. Of the 31 patients with Grade 1/ Grade 2 ILD who were rechallenged with osimertinib, 27 patients (87.1%) did not experience a recurrence of ILD. Of the 4 patients who developed a subsequent episode of ILD, 1 patient developed Grade ≥3 ILD with an unknown outcome. The remaining 3 patients experienced Grade 1 or Grade 2 ILD and recovered or were recovering.

If ILD/pneumonitis of any grade is identified during neoadjuvant treatment, osimertinib/placebo (Arm 1 or 2) or osimertinib (Arm 3) must be permanently discontinued.

During the EFS follow-up period, participants receiving adjuvant osimertinib who experience any of the following AEs will be permanently discontinued from adjuvant osimertinib:

- CTCAE Grade 3 or higher ILD/pneumonitis
- CTCAE Grade 2 ILD/pneumonitis where symptoms have not resolved within 4 weeks after dose interruption
- Recurrent symptomatic ILD/pneumonitis following prior dose interruption and study intervention rechallenge.

Patients with new onset Grade 1 or 2 ILD/pneumonitis during adjuvant osimertinib

treatment that does not meet the discontinuation criteria above may, at the investigator's discretion, continue or reinitiate adjuvant osimertinib per the ILD/pneumonitis dosing modification and toxicity management guideline below in Table 17. In patients who continue or reinitiate adjuvant osimertinib after Grade 1 or 2 ILD/pneumonitis, investigators must collect all AEs (not only SAEs and AESIs) after continuation or reinitiation of adjuvant osimertinib until it has been discontinued.

Table 17 Dosing modification and toxicity management guideline for ILD/pneumonitis during treatment with adjuvant osimertinib [a]

Grade of the Event (NCI CTCAE version 5.0)	Dose modification	Toxicity management
Any Grade	-	• Monitor participants for signs and symptoms of pneumonitis (new onset or worsening shortness of breath or cough). Participants' status should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures, as described below. • Initial work up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion) laboratory work-up and high-resolution CT scan.
Grade 1 Asymptomatic, clinical or diagnostic observations only, intervention not indicated. *Note*: If the participant remains asymptomatic, then the event should be considered as Grade 1 even if prophylactic corticosteroid treatment is given to prevent symptoms from developing.	**No dose modification required; however** • Holding study intervention may be considered as clinically appropriate and during diagnostic work-up for other aetiologies. • If study intervention is held, it is recommended to restart study intervention within 4 weeks after interruption. Consult with AstraZeneca study physician or delegate if the interruption is longer than 4 weeks.	• Perform investigations as clinically appropriate • Treat in accordance with local clinical practice • Consider prophylactic treatment with corticosteroids to prevent worsening of ILD • If the participant continues study intervention after diagnosis of Grade 1 ILD, monitor the participant and closely follow up 2 to 4 days after diagnosis for onset of clinical symptoms. Continue to monitor closely thereafter: – Perform additional assessments as required – Consider additional imaging – Additional monitoring such as additional visits or phone calls are recommended • In participants who restart study intervention after diagnosis of Grade 1 ILD and study intervention interruption, monitor and closely follow-up 2 to 4 days after study intervention has restarted, and at periodic intervals thereafter: – Perform additional assessments as required – Consider additional imaging – Additional monitoring such as additional visits or phone calls are recommended

Table 17 Dosing modification and toxicity management guideline for ILD/pneumonitis during treatment with adjuvant osimertinib [a]

Grade of the Event (NCI CTCAE version 5.0)	Dose modification	Toxicity management
		• Follow Grade 2 guidelines if ILD becomes symptomatic.
Grade 2 Symptomatic, medical intervention indicated, limiting instrumental ADL.	**Hold study intervention until resolution of symptoms** The decision to re-initiate study intervention will be based on treating physician's clinical judgment and following endorsement from the AstraZeneca study physician or delegate physician. Consider re-initiating study intervention if symptoms of ILD have resolved within 4 weeks after study intervention interruption. In such cases, it is recommended to restart study intervention within 4 weeks after interruption. Study intervention must be permanently discontinued if Grade 2 pneumonitis symptoms have not resolved within 4 weeks after study intervention interruption. Study intervention can be reinitiated alongside ongoing steroid treatment for ILD/pneumonitis, and then steroids can be tapered down or withdrawn as clinically appropriate. Re-initiation at either osimertinib 80 mg/placebo QD or at a reduced dose of osimertinib 40 mg/placebo QD can be considered, as clinically appropriate, and in agreement with the AstraZeneca study physician or delegate physician. If ≥Grade 2 pneumonitis (symptomatic) occurs following re-initiation of study intervention, the study intervention must be permanently discontinued.	• Monitor and closely follow up according to the participant's clinical presentation, including additional assessments as clinically indicated (in accordance with clinical practice). • Treat in accordance with local clinical practice. • Recommend treatment with corticosteroids until improvement, followed by tapered corticosteroid dosing until withdrawn. • In participants who restart study intervention after symptoms of ILD have resolved, monitor and closely follow-up 2 to 4 days after study intervention has restarted, and at periodic intervals thereafter: – Perform additional assessments as required – Consider additional imaging as clinically indicated – Additional monitoring such as additional visits or phone calls are recommended

Table 17 Dosing modification and toxicity management guideline for ILD/pneumonitis during treatment with adjuvant osimertinib [a]

Grade of the Event (NCI CTCAE version 5.0)	Dose modification	Toxicity management
Grade 3 or 4 **Grade 3** Severe symptoms, limiting selfcare ADL; oxygen indicated. *Note*: Participants given oxygen in the absence of symptoms or hypoxia (ie, oxygen is not indicated, but given as a precaution) can be considered to have a Grade 1 or Grade 2 ILD event, as applicable, and do not require permanent discontinuation of study intervention. **Grade 4** Life-threatening respiratory compromise, urgent intervention indicated, eg, tracheostomy or intubation.	**Permanently discontinue study intervention**	• Treat in accordance with local clinical practice. • Recommend treatment with corticosteroids until improvement, followed by tapered corticosteroid dosing until withdrawn.

[a] Includes ILD and other pneumonitis events (Interstitial lung disease, Pneumonitis, Acute interstitial pneumonitis, Alveolitis, Diffuse alveolar damage, Idiopathic pulmonary fibrosis, Pulmonary fibrosis). The dose modification and toxicity management of the ILD/pneumonitis event followed in Table 17 must be aligned with the highest Grade of the ILD/pneumonitis event recorded in the eCRF.

Abbreviations: ADL, Activities of daily living; CT, Computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ILD, Interstitial lung disease; QD, Once daily; NCI, National Cancer Institute

8.5.6.4.2 QTc prolongation

In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec, or recovery to baseline if baseline QTcF is ≥ 481 msec, and then restarted at a reduced dose of 40 mg QD/placebo. If the toxicity does not resolve to ≤CTCAE Grade 1 within 21 days, the patient will be permanently withdrawn from study treatment.

8.5.6.4.3 Keratitis

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

8.5.6.4.4 Erythema multiforme, Stevens-Johnson syndrome, and Toxic epidermal necrolysis

Case reports of Erythema multiforme (EM) and toxic epidermal necrolysis (TEN) have been uncommonly reported, and Stevens-Johnson syndrome (SJS) have been rarely reported, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM, SJS, and TEN. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted. Osimertinib should be discontinued immediately if SJS or TEN is diagnosed.

8.5.6.4.5 Aplastic anaemia

Rare reports of aplastic anaemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, and pallor. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anaemia.

8.5.6.4.6 Changes in cardiac contractility

Across clinical trials, LVEF decreases ≥10% and a decrease to <50% occurred in 3.9% (35/908) of patients treated with osimertinib who had baseline and at least 1 follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. However, LVEF will be monitored in all patients by way of Echo/MUGA scans.

8.5.6.4.7 Haematological parameters

Patients meeting any of the criteria below must have osimertinib/placebo interrupted until the toxicity resolves to ≤CTCAE Grade 2. Osimertinib/placebo may be restarted at the same dose (80 mg/placebo) or a lower dose (40 mg/placebo) at the discretion of the investigator.

- Febrile neutropenia
- Grade 3 neutropenia with an associated ≥Grade 3 infection or suspected infection in the absence of fever
- Grade 4 neutropenia
- Grade 3 thrombocytopenia with ≥Grade 2 bleeding
- Grade 4 thrombocytopenia

8.6 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. See Appendix C for further details on the handling of human biological samples.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

8.6.1 Pharmacokinetics

Whole blood samples will be collected for measurement of plasma concentrations and PK parameters of osimertinib and its metabolite AZ5104, at the timepoints specified in the SoA (Table 1 – Neoadjuvant period).

Sample collection will occur at pre-dose (within 1 hour of dosing of the first study drug) and 0.5 to 2 hours post-dose, on C2D1 (D22 if there is no treatment delay or later in case of delays) and C3D1 (D43 if there are no treatment delays or later in case of delay). For chemotherapy-containing treatment arms (Arms 1 and 2), osimertinib PK samples at C2D1 and C3D1 should be collected on the day of the chemotherapy dosing for that cycle. For osimertinib/placebo PK (Arms 1 to 3), sample collection should only be taken if the patient has received 7 days of continuous osimertinib/placebo dosing prior to that specific PK measurement. If the dosing for chemotherapy or osimertinib/placebo is altered due to interruption or modified for any other reason, then the collection of this PK sample should be performed at the next scheduled dosing of chemotherapy and osimertinib.

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, provided they are aligned with local regulations. Instructions for the collection and handling of biological samples will be provided

by the Sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample along with the dosing time on the PK day and the day prior to the PK day will be recorded.

Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual

Plasma samples collected for analyses of osimertinib (and AZ5104) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Only osimertinib-dosed patients will be analysed in the bioanalytical lab using a validated bioanalytical method. The unblinding to identify the samples will only be available to the bioanalytical lab and this information along with the concentration data will not be shared with any other study personnel until after database lock.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6.1.1 Determination of drug concentration

Samples for determination of osimertinib (and AZ5104) concentration in plasma will be analysed by Covance BioA Laboratory on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. All samples within the known stability of the analytes of interest (ie, osimertinib and AZ5104) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the PK samples may be subjected to further analyses by AstraZeneca to further investigate the presence and/or identity of additional drug metabolites and/or correlate PK with other primary, secondary, and exploratory endpoints in patients treated with osimertinib. These additional analyses are not applicable for China as per local regulations. Any results from such analyses may be reported separately from the CSR.

Full details of the analytical method used will be described in a separate bioanalytical report.

8.6.1.2 Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

PK samples may be disposed of or destroyed and anonymised by pooling for further analysis. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual PK samples may be used for future exploratory biomarker research (in this case, residual PK samples will be shipped to AstraZeneca-assigned Biobank).

All PK samples and PK testing residual samples collected in China will be stored and disposed of according to local laws and regulations. PK samples collected in China will be destroyed after finalization of bioanalytical report or completion of CSR.

8.6.2 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6.3 Surgical specimen collection

The surgical specimen collected during surgical resection (following neoadjuvant treatment) is required for MPR and pCR assessment as well as diagnostic and exploratory testing. The surgical specimen should be submitted to the central pathology laboratory, ideally within 8 weeks after surgery. Refer to the pathology manual for further details.

8.7 Human Biological Samples: Biomarkers

This study involves the mandatory and optional provision of samples for both prospective and retrospective biomarker analyses, as detailed in the SoA (Table 1 and Table 2), Table 18 (mandatory samples for biomarkers analysis), and Table 19 (optional samples for biomarker analysis).

Details of mandatory biomarker analyses (including prospective EGFR mutation status testing on FFPE tumour samples, which will be used for study eligibility assessment), and optional biomarker analyses are described in Section 8.7.1 and Section 8.7.2, respectively.

Additional exploratory analyses may be undertaken on the data generated from patient's samples to identify other biomarkers of sensitivity and resistance to study treatments and our

understanding of cancer and may be used to support diagnostic development. Samples collected in China will not be used for additional exploratory biomarker analyses until approved by relevant local authorities.

Instructions for the collection and handling of biological samples are provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of human biological samples, see Appendix C.

Where permitted by local regulations, samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated. In China, samples for exploratory analyses will only be collected after approval by relevant local authorities. Remaining samples in China will be destroyed or repatriated maximally 5 years from the date of issue of the final CSR.

8.7.1 Collection of mandatory samples for biomarker analysis

By consenting to participate in the study the subject consents to participate in the mandatory research components of the study. Samples for biomarker research are required and will be collected from all patients in this study, at the timepoints specified in Table 18 and the SoA (Table 1 and Table 2).

Table 18 Mandatory samples and timepoints for biomarker analysis

Timepoint	Sample type *(analysis purpose)*					Notes
	Tumour FFPE sample (tissue biopsy or FNA [f]) *(central EGFR mutation analysis)*	**Remaining tumour FFPE sample** *(exploratory analysis)*	**Plasma** *(central EGFR mutation analysis, MRD, ctDNA testing)*	**Whole blood** *(CHIP & HLA analysis)*	**Surgical tumour FFPE tissue** *(MPR & exploratory analysis)*	
Screening	X	X [b]	X (EGFR testing only)			Baseline sample
Neoadjuvant C1D1			X [c] (MRD, ctDNA testing only)	X [c]		Baseline sample
Pre-surgical assessment			X [c] (MRD, ctDNA testing only)			End of neoadjuvant treatment
Surgery					X [e]	Surgery after neoadjuvant therapy

Timepoint	Sample type *(analysis purpose)*					Notes
	Tumour FFPE sample (tissue biopsy or FNA [f]) *(central EGFR mutation analysis)*	**Remaining tumour FFPE sample** *(exploratory analysis)*	**Plasma** *(central EGFR mutation analysis, MRD, ctDNA testing)*	**Whole blood** (*CHIP & HLA analysis)*	**Surgical tumour FFPE tissue** *(MPR & exploratory analysis)*	
EFS follow-up period			X [c] (MRD, ctDNA testing only)			Samples taken at Adjuvant IP-osimertinib treatment decision visit [d] and Week 12, then in alignment with imaging assessments [a]

[a] Adjuvant IP-osimertinib treatment decision visit, Week 12, Week 24, then every 24 weeks until Week 264 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.

[b] In China, residual unstained tissue samples will not be used for other purposes unless approved by China local relevant authorities.

[c] Samples are optional and are not collected or analysed in China until after approval of relevant local authorities.

[d] To be collected prior to the initiation of adjuvant IP osimertinib, ideally on the same day, but may be collected up to 7 days prior to this visit.

[e] In China, surgical specimen tissue for exploratory biomarker and NGS testing is optional and will only be collected or analysed after the approval of relevant local authorities.

[f] Tumour FFPE FNA sample collected per SoC prior to or during screening is acceptable where tumour FFPE tissue biopsy is not available.

8.7.1.1 Screening tumour and plasma samples for central EGFR testing

In this study patients can be considered eligible for inclusion based upon either (i) prospective central tumour tissue analysis of EGFR mutation status performed using the cobas® EGFR Mutation Test v2; or (ii) a pre-existing positive local EGFR test result obtained using the cobas® EGFR Mutation Test v2 in CLIA-certified (for US sites) or accredited laboratories (for sites outside of the US) on tissue sample according to its instructions for use or using FoundationOne® CDx; or (iii) in the case that neither tumour tissue sample with preserved tumour tissue architecture nor pre-existing cobas® EGFR Mutation Test v2, nor FoundationOne® CDx EGFR test result from tumour sample per IFU is available, EGFR mutation status can be centrally confirmed, when permitted by AstraZeneca, in a tumour FFPE FNA sample, collected per SoC prior to, or during, screening, using the Idylla™ EGFR Mutation Test. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment. Patient will only undergo tumour biopsy if it is considered a medically acceptable risk by the investigator.

For patients entering the study based upon a pre-existing local test result, the pre-existing local EGFR laboratory results and the test method used should be collected and maintained as a source document and captured in the eCRF. These patients should provide a FFPE tumour tissue (if available) for retrospective testing with the cobas® EGFR Mutation Test v2 in a central laboratory (central test result will not be mandated before randomization). This includes patients whose local positive test result was obtained from the cobas® EGFR Mutation Test v2. For patients who are enrolled based on tumour FFPE FNA samples, provision of additional tumour FFPE FNA samples, if available, is requested for future confirmation testing using an FDA approved FNA test. The total number of tumour FFPE FNA samples required can be found in the Laboratory Manual.

In addition, all patients are mandated to provide a plasma sample during screening for retrospective central testing of EGFR mutations in order to assess concordance with tissue test results and to assess outcome based on plasma positivity. However, this plasma test result will not be used for study entry criteria. Plasma sample (mandatory for all patients) should be provided for central testing with the cobas® EGFR Mutation Test v2 as outlined below. Further guidance is provided in the Laboratory Manual.

The Investigator will be asked to provide:

- FFPE tumour tissue blocks or tumour FFPE FNA block, not older than 12 months, or
- Unstained sections from FFPE tumour tissue block or tumour FFPE FNA block (the absolute minimum number of slides will be described in the Laboratory Manual), mounted on glass slides. The unstained sections for both FFPE tumour tissue and tumour FFPE FNA should not be more than 60 days old. Each section is to be 5 µm thick for both FFPE tumour tissue and tumour FFPE FNA.
- A plasma sample: guidance is provided in the Laboratory Manual regarding the blood collection, volume requirement, processing to plasma and storage.

Tumour tissue blocks should be provided wherever possible for further analysis, except for China study sites, who will submit only unstained sections from the tissue block. EGFR mutation testing residual unstained tumour and plasma samples collected in China will be destroyed or repatriated maximally 5 years after the indication of this study is approved for marketing in China. Remaining tumour, plasma and DNA extracts of EGFR testing samples may also be used for exploratory biomarker analysis and to support diagnostic development (where approved according to local regulations.).

Any biopsy, including needle core biopsy sample in which the tissue architecture is maintained are acceptable for central laboratory testing by the cobas® EGFR Mutation Test v2. If such a biopsy sample is not available, tumour FFPE FNA samples, if available, are

acceptable for central laboratory testing by the Idylla™ EGFR Mutation Test, when permitted by AstraZeneca.

If the first tumour sample submitted for central testing does not give valid test result due to test failure, a further tumour sample may be submitted for central testing. Re-tests are not permitted if the central testing result is EGFR mutation negative for Ex19del and L858R.

While the eligible EGFR mutations for this study are Ex19del and L858R, other EGFR mutations (T790M, G719X, Exon20 insertions, S768I and L861Q) will be reported as part of the local EGFR test result and should be captured in the eCRF. Similarly, Ex19del, L858R and other EGFR mutations will be reported from the central testing of the sample.

8.7.1.2 Collection of other mandatory samples for exploratory biomarker analysis

Biomarker analyses may be performed by AstraZeneca or designated organisations on DNA and/or tissue (from mandatory screening and surgical tumour tissue, blood, and plasma samples for 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 where permitted by local regulation. See Table 18 for details of sample requirements and collection timepoints.

Samples will be tested for minimal residual disease (MRD) to evaluate their association with the observed clinical responses of MPR and EFS to each neoadjuvant intervention therapy. Additionally, MRD testing will be used to evaluate molecular signals of disease progression in the EFS follow-up period and will be associated to MPR, EFS, and adjuvant therapies. To enable MRD testing, tumour tissue, plasma, and blood samples are required as described in the following subsections. Additional exploratory analyses may be performed as described.

<u>These samples are optional in China and will not be collected or analysed until approved by China local relevant authorities.</u>

8.7.1.2.1 Tumour markers

Tumour samples and derivatives obtained as part of screening procedures, including residual DNA and/or tumour samples from mandatory central EGFR testing, may be used to establish tumour genomic landscapes via next-generation sequencing (NGS). This DNA/tumour sample may be obtained from either the screening sample or from the surgical resection. The tumour genomic landscapes will be used to inform MRD assays. These data will also support exploratory biomarker analyses between genomics and clinical responses.

Based on the availability of screening and surgical tumour sample, additional exploratory biomarker work may be performed. This may include, but is not limited to, analysis of DNA,

RNA, and/or protein from tumour or tumour-infiltrating lymphocytes to better understand markers of drug response, resistance, and tolerance.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics development.

Please refer to the Laboratory Manual for further details regarding sample collection, shipping, storage, and sample requirements for central testing including minimum FFPE slide number.

These samples will not be used outside the approved scope from relevant local authorities in China.

8.7.1.2.1.1 Soluble factors - plasma

The concentrations of a panel of relevant cytokines, chemokines, and other immune-related markers may be assessed. Plasma may also be used to evaluate mutant circulating tumour DNA (ctDNA). Overall mutational burden and/or somatic mutations/genomic alterations in plasma may be assessed and will be correlated with response. Additionally, tumour mutational burden (TMB) and MSI may be evaluated by ctDNA in the plasma for all patients, both pre- and post-treatment.

MRD technolog(y/ies) will be applied to plasma samples obtained from blood to test for molecular evidence of disease. This will include samples from the neoadjuvant (pre-treatment, pre-surgery) and EFS follow-up period of the study (at each follow-up imaging timepoint), as specified in the SoA (Table 1 and Table 2) and Table 18. Data from these assays may also support additional exploratory biomarker work to explore associations between genomic alterations and clinical responses and therapeutic resistance.

8.7.1.2.1.2 Whole blood for DNA

AstraZeneca or designated organisations will investigate in the whole blood sample the following genes: HLA class I and class II. This analysis is required to examine these key immune related genes and their potential association with adverse events and clinical efficacy. Additionally, genomic analysis will be used to improve the identification of mutations derived from the patient's tumour. The intent is to remove genetic alterations not of tumour origin such as: germline variants and clonal haematopoiesis of indeterminate potential (CHIP). This analysis is necessary to fully enable highly sensitive MRD technologies.

8.7.2 Collection of optional biomarker samples

Collection of optional samples for biomarker research is also part of this study, as specified in the SoA (Table 1) and Table 19, and is subject to agreement to optional consent.

Based on the availability of screening tumour samples and surgical tumour tissue, additional exploratory biomarker work may be performed. This may include, but is not limited to, analysis of DNA, RNA, and/or protein from tumour or tumour-infiltrating lymphocytes to better understand markers of drug response, resistance, and tolerance.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics development.

Please refer to the Laboratory Manual for further details regarding sample collection, shipping, and storage.

Table 19 Optional samples and timepoints for biomarker analysis

Timepoint	Sample type *(analysis purpose)*		Notes
	Additional tumour FFPE tissue *(exploratory analysis)*	**Plasma sample** *(MRD and ctDNA testing)*	
Disease progression [a]	X [b]	X [c]	Progression sample

[a] Disease recurrence detected outside of a scheduled visit should be entered as an unscheduled visit.

[b] Samples not collected in China.

[c] Plasma samples are only collected or analysed in China after approval by relevant local authorities.

8.8 Optional Genomics Initiative Sample

Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

Collection of an optional sample for genomics initiative research is also part of this study, and is subject to agreement in the ICF addendum. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. One 6 mL blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. This blood sample will be collected pre-dosing on Day 1. If, for any reason, the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetic analysis during the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D and the Laboratory Manual.

The optional genetic sample will not be collected in China.

8.9 Medical resource utilization and health economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The assessment of health care resource use will increase the understanding regarding the relationship between treatment and tumour-related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction or bleeding. This will be captured and analysed to inform submissions to payers.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

8.10 Study Participant Feedback Questionnaire

This trial will include an optional anonymized 'Study Participant Feedback Questionnaire' for patients to provide feedback on their clinical trial experience (see Appendix F).

Questionnaires should be completed on D1 (prior to the first dose of study treatment), at C3-D1, and at the Week 24 visit in the EFS follow-up period (see Table 1 and Table 2). The patients will complete the questionnaires using an electronic tablet (or via a website) during clinic visits.

Individual patient level responses will not be reviewed by investigators. Responses would be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the patients' disease, symptoms, treatment effect or adverse events and therefore would not be trial data.

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives. All personnel involved with the statistical analysis of the study will remain blinded until database lock and CSP deviations have been identified. A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized around the time of first patient in (FPI).

9.1 Statistical hypotheses

The hypothesis of interest with regards to the efficacy is:

- H0: No difference between osimertinib (either as monotherapy or in combination with chemotherapy) and SoC.
- H1: Difference between osimertinib (either as monotherapy or in combination with chemotherapy) and SoC.

9.2 Sample size determination

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

- Placebo 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 1); or
- Osimertinib 80 mg once daily (QD) + investigator's choice of chemotherapy (as above) (Arm 2); or
- Osimertinib 80 mg QD as monotherapy (Arm 3).

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. Details of the sample size calculations are shown below. For the multiple testing procedure and for details of the alpha allocation and alpha spend, refer to Section 9.4.5.

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 laboratory. The final analysis for the MPR endpoint will occur when the last patient has had the opportunity to complete surgery and the MPR assessment per central pathology laboratory (approximately 6 months after the last patient is randomised). The study has an approximate 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).

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full analysis set	All patients who are randomized in the study. The FAS will be used for all the efficacy analyses except DFS.
Resected analysis set	All patients in the FAS who underwent and completed definitive surgical resection The resected set will be used for DFS endpoint.
Safety analysis set	All randomized patients who received at least 1 dose of study treatment.
PK analysis set	All patients in the SAS who have at least 1 measurable PK concentration without any protocol deviation that affects the PK, supported by the relevant date and time of this sample; and, for each time a PK sample was taken, 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.

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalised by first patient in and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued the study treatment, COVID-19 testing results, and other protocol deviations) may be generated. More details will be provided in the SAP.

All efficacy analyses will be performed on the FAS population, with the exception of DFS analysis which will use the resected analysis set, and the safety analysis set will be used for all safety and tolerability tables, figures, and listings, except where expressly noted.

9.4.1 Efficacy

9.4.1.1 Primary endpoint: Major Pathological Response (MPR)

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. “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.

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.

Per the primary analysis, MPR will be calculated as number of patients with MPR response in the FAS (ie, all randomised patients). A sensitivity analysis will be conducted excluding patients with MPR "non-evaluable" from the denominator. More details on how MPR will be derived will be provided in the SAP.

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 mainland China] and Chinese living in mainland 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 the significance level in Figure 4 and Section 9.5). The FAS population will be used.

Subgroup analyses will be conducted by comparing MPR between the experimental arm (either Arm 2 or Arm 3) and the control (Arm 1) in 3 stratification factors: disease stage, race and mutation type. Additional details on subgroups are provided in the SAP.

9.4.1.2 Secondary endpoint: Pathological Complete Response (pCR)

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. Patients will only be considered to have pCR if they also have an R0 margin result. "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 and will be captured as "non-evaluable" or "missing," as appropriate.
- Patients with a R1/R2 margin result or those without a margin result.

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.

The pCR statistical analysis 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.

9.4.1.3 Secondary endpoint: Event-free survival (EFS)

EFS is the key secondary endpoint and defined as the time from the date of randomisation until an event occurs (ie, date of event —date of randomisation +1). An event is defined as

documented disease progression that precludes surgery or prevents completion of definitive surgery; recurrence or a new lesion, local or distant (a new primary malignancy, confirmed by pathology if clinically feasible, is not considered to be an EFS event); death due to any cause. After completion of the neoadjuvant period, patients who do not undergo surgery for reasons other than progression or who do not 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 progression that precludes surgery 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. Patients will be followed for up to 42 months after the last patient is randomised.

Final analysis of EFS will be conducted when all patients have had the opportunity for at least 3 years follow-up post-surgery**,** ie, 42 months after the last patient randomised.

The analysis for EFS will be performed using the log-rank test stratified by disease stage, mutation type and race for the generation of the p-values and the treatment difference measured by a HR and 100 * (1-alpha)% CI will be obtained directly from the U and V statistics (Berry et al 1991). The significance level is provided in Figure 4 and Section 9.5.

A KM plot of EFS will be presented by treatment group.

The assumption of proportionality will be assessed. In the event of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining the plots of complementary log-log (event times) versus log (time) and, if necessary, a time-dependent covariate will be fitted to assess the extent to which this represents random variation.

Patients with no event recorded will be censored at their last known disease assessment.

Subgroup analyses will be conducted comparing EFS in 3 stratification factors: disease stage, race and mutation type. Additional detail on subgroups are provided in the SAP.

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 EFS will not be analysed. In this case, only descriptive summaries will be provided.

A sensitivity analysis will be performed if EFS is assessed by blinded independent central review, further details will be provided in the SAP.

9.4.1.4 Secondary endpoint: Overall Survival (OS)

OS will be defined as the time from the date of randomisation until death due to any cause (ie, date of death – 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. 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.

The OS analysis will be performed to estimate the treatment difference in OS via HR adjusted the stratification factors of disease stage, mutation type and race. The HR and 95% CI will be obtained directly from the U and V statistics (Berry et al 1991). A 5-year landmark analysis will also be conducted. No statistical testing of OS will be conducted.

9.4.1.5 Secondary endpoint: Disease Free Survival (DFS)

DFS will only be evaluated on the resected analysis set i.e. patients who underwent and completed definitive surgical resection following neoadjuvant treatment and are disease free. 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, whichever occurs first.

Pathological confirmation from biopsied lesions, if performed according to investigator's' 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 of the first post-surgical scan or the latest date of evaluable disease assessment after the surgical resection date.

DFS will be evaluated at the same timepoints as the EFS endpoint. It will be performed using KM estimates of DFS and detailed further in the SAP.

9.4.1.6 Secondary endpoint: Downstaging

Downstaging is assessed in accordance with the American Joint Committee on Cancer 8th edition TNM staging system. Pathological downstaging is defined as baseline N2 patients becoming N1/N0 or N1 to N0 at the time of surgery. Downstaging will only be formally assessed for patients with pathological staging available at both timepoints.

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”. The analysis of 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.

9.4.2 Clinical outcome assessments

9.4.2.1 EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall quality of life will be assessed using EORTC QLQ-C30 and QLQLC13. Questionnaires will be scored according to published guidelines or the developer’s

guidelines, if published guidelines are not available. All PRO analyses will be based on the FAS. Further details of the statistical analyses including details of Mixed effect Models for Repeated Measures (MMRM) modelling will be given in the SAP.

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), and a global measure of health status. The QLQ-LC13 is a lung-cancer-specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea, and site-specific pain), treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication. With the exception of a multi-item scale for dyspnoea, all are single items. The dyspnoea scale will be used only if all 3 items have been scored; otherwise, the items are treated as single-item measures.

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 (QoL) scale according to the EORTC QLQ-C30 Scoring Manual (EORTC QLQ-C30 Scoring Manual, Third Edition) and EORTC QLQ-LC13 instructions. Higher scores on the global health status/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of 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 reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimised.

Compliance with the EORTC QLQ-C30 and EORTC QLQ-LC13

Compliance with the EORTC QLQ-C30 and EORTC QLQ-LC13 will be calculated separately for each questionnaire.

Clinically meaningful changes

Changes in score compared to baseline will be evaluated.

Time to symptom and HRQL/function deterioration (QLQ-C30 and QLQ-LC13)

Time to deterioration in symptoms, functioning and global health status/QoL will be evaluated.

Improvement in symptom and HRQL (QLQ-C30 and QLQ-LC13)

Improvement in symptoms, functioning and global health status/QoL will be evaluated.

9.4.3 Safety analyses

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, ECOG PS, and ophthalmologic assessment. These will be collected for all randomized patients.

Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data.

9.4.4 Other analyses

9.4.4.1 Pharmacokinetics and pharmacodynamics

Details of PK, population PK, pharmacodynamic, PK/pharmacodynamic relationships, and and/or exposure response/safety analyses will be described in the SAP finalized before database lock. The population PK analysis and pharmacodynamic analyses may be presented separately from the main CSR.

9.4.4.2 EQ-5D-5L health state utility

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). 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. These data will be converted into a weighted health state index by applying scores from EQ5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. 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.

9.4.4.3 Cure rate

The cure rate is defined as the percentage of people in the study who are still alive and disease free for a certain period of time after they finished the surgery. For this analysis, the DFS 5-year landmark will be calculated at the same time as OS analysis, and will be summarised (using the KM curve) and presented by treatment arm. Patients will be followed-up for approximately 5.5 years after the last patient is randomised to allow opportunity for all patients to be followed-up 5 years post-surgery.

9.4.5 Methods for multiplicity control

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 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.

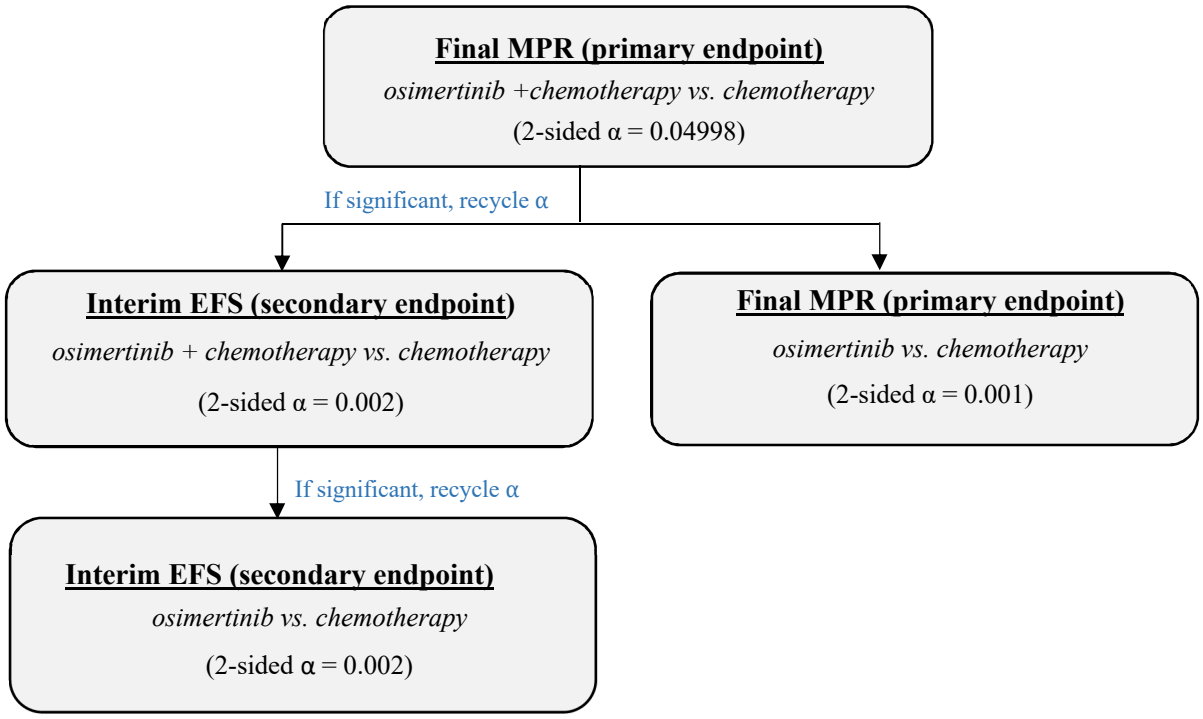
As 2 analyses of EFS are planned, the Haybittle-Peto boundary approach will be used to maintain an overall 2-sided 4.898% type I error with 0.2% alpha spent on the EFS interim analysis and the remaining alpha spent at the final EFS analysis to control overall 2-sided 4.898% type I error. The final analysis 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 is calculated as the number of patients finished

the surgery at the analysis time-point divided by the total number of patients at the final analysis time-point.

The multiple testing procedure (as shown in Figure 4) 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 4 Multiple testing procedure



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

9.5 Interim analyses

The SAP will describe the planned interim analyses in detail.

An 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 randomised patients have had the opportunity to complete surgery and the MPR assessment per central pathology laboratory. Given the futility analysis is considering efficacy data, a small amount of alpha 0.001% (2-sided) will be assigned to this analysis (under Haybittle-Peto boundary) for MPR testing on each treatment arm against the

control arm, respectively. This interim analysis will be conducted by the IDMC and recommendation regarding continuing each treatment arm will be made to the sponsor.

The final analysis of MPR will occur when the last patient has 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 analyses for the primary endpoint.

For the EFS endpoint, there is 1 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.

9.5.1 Independent data monitoring committee (IDMC)

An IDMC will be utilised for this study. Section A 5 provides more details on the rationale for and the remit of the committee.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca study representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

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 randomized 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 procedures and processes can be found in the IDMC Charter.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the Investigator's Brochure or in the investigator site file and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.
- If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.
- If a patient's partner becomes pregnant during or within 4 months after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.
- Patients who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

- The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law.
- Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.
- Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[3] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

[3] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission.

Notification of personal Data Breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (i.e Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be

addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

- A description of this clinical study will be available on www.astrazenecaclinicaltrials.com [http://www.clinicaltrials.gov and http://euclinical trials.eu/] as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.
- Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A 7 Data quality assurance

- All patient data relating to the study will be recorded on printed or electronic Case Report Form (CRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the medical oversight plan.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the

written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and site closure

- The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.
- The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further study intervention development
- If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

- Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, 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 anomaly or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above

AEs for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that

is being treated by the IP under study and is not the development of new, or progression of existing, metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale

The grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route, dose (error greater than +/- 10%), or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet

- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology [IRT]/ Randomisation and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP/study intervention or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study interventions or AstraZeneca NIMPs, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or delegate.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented, and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

C 3.1 Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) (https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx) classifies infectious substances into 3 categories: Category A, Category B or Exempt

- **Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
- **Category A pathogens** are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.
- **Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:
  - UN 3373 – Biological Substance, Category B
  - are to be packed in accordance with UN3373 and IATA 650
- **Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

Clinical study samples will fall into Category B or exempt under IATA regulations

Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).

Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.

The results of genetic analyses may be reported in the Clinical Study Report (CSR) or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on osimertinib continues, but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

D 2.1 Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Transfusion of non-leukocyte depleted blood or blood component within 120 days of genetic sample collection

D 2.2 Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

D 2.3 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients prior to the first dose of study therapy. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

D 2.4 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated

organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the patient enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

D 2.5 Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix B.

D 2.6 Informed consent

The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

D 2.7 Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

D 2.8 Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other

researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

D 2.9 Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Definition of women of childbearing potential and highly effective contraceptive methods

E 1 Definition of women of child-bearing potential

- **Women of Childbearing Potential (WoCBP):** Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.
- **Women NOT of Childbearing Potential**: Women who are permanently or surgically sterilised or post-menopausal (definitions below):
  - Permanent sterilisation: includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).
  - Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (eg. undergo pregnancy testing etc, as required by the study protocol).
  - Women will be considered post-menopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women under 50 years old will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.
  - Women aged 50 years or more will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.

E 2 Highly effective contraception methods

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (eg. less than 1 percent per year) when used consistently and correctly.

All women of child bearing potential must have a negative serum pregnancy test result at Visit 1. Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial.

Generic names and examples of trade names are given. As trade names may vary, investigators should check the generic name of any contraception to ensure suitability.

Highly effective contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine Device (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) Levonorgestrel Intra Uterine System (eg, Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (eg, Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (eg, ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone-based pill

E 3 Unacceptable contraception methods

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

Appendix F Patient-reported outcomes questionnaires and study participants feedback questionnaire

F 1 EORTC QLQ-C30

Patient Reported Outcomes Questionnaire: EORTC QLQ-C30 was removed due to copyrights

Patient Reported Outcomes Questionnaire: EORTC QLQ-C30 was removed due to copyrights

F 2 EORTC QLQ-LC13

Patient Reported Outcomes Questionnaire: EORTC QLQ-LC13 was removed due to copyrights

F 3 EQ-5D-5L

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights

F 4 Study Participants Feedback Questionnaire

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Appendix G Guidance regarding potential interactions with concomitant medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

G 1 Drugs inducing CYP3A4 metabolism that AstraZeneca strongly recommend are not combined with study treatment

Osimertinib is metabolised by the CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 should not be used during this study for any patient receiving study treatment.

Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to study treatment start
Carbamazepine, phenobarbital (phenobarbitone), phenytoin, rifampicin, rifabutin, rifapentine, St John's Wort	3 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Contact AstraZeneca with any queries on this issue.

G 2 Medicines whose exposures may be affected by osimertinib that AstraZeneca considers may be allowed with caution

Osimertinib may increase the concentration of sensitive BCRP and P-gp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive P-gp substrate, fexofenadine, are increased).

Exposure, pharmacological action, and toxicity may be increased by osimertinib

Warning of possible interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to the full prescribing information for all drugs prior to co-administration with study treatment.
Sulfasalazine	
Doxorubicin	
Daunorubicin	

Warning of possible interaction	Advice
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

G 3 Drugs that prolong QT interval

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics (ArizonaCert) website: https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening, the drugs that patients are currently using (prescription and non-prescription) should be checked against the ArizonaCert website. In addition, drugs intended for use during study treatment should be checked against the website.

G 3.1 Drugs with a known risk of Torsades de Pointes

Drugs in this category are known to prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

G 3.1.1 Before study treatment

These drugs **must** have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in the table below.

G 3.1.2 During study treatment

It is recommended that these drugs are not co-administered with IP (osimertinib/placebo) and for a period of 2 weeks after discontinuing study treatment; however, if it is considered essential for patient management to co-administer these drugs with IP, close monitoring of ECGs and electrolytes is recommended.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such, Investigators are recommended to search the CredibleMeds® website (https://www.crediblemeds.org/) to provide the most up to date information.

Drugs with a known risk of TdP [a]

Drug name	Withdrawal period prior to study treatment start [b]
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide[c], ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

[a] This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/)

[b] Values determined from comprehensive review (internal to AZ) of each compounds PK half-life and determination of the washout period.

[c] Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

G 3.2 Other TdP risk categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management, and the patient has been stable on therapy. Close monitoring of ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome (CLQTS) are excluded** from this study.

G 3.3 Guidance regardless of TdP risk category

During study treatment and for a period of 2 weeks after discontinuing study treatment, if it is considered essential for patient management to co-administer drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring of ECGs and electrolytes is recommended.

Appendix H Calculated Creatinine Clearance

H 1 Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{weight}^{b}) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{weight}^{b}) \times 1.0}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

H 2 Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{weight}^{b}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{weight}^{b}) \times 0.85}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

Calculation of creatinine clearance from 24-hour urine collection:

$$\text{CrCl (mL/min)} = \frac{\text{urine creatinine} \times \text{24-hour urine volume (ml)}}{\text{serum creatinine} \times 1440}$$

Source: Doolan et al 1962

Serum and urine creatine concentration must be in same units. The use of internet-based calculators is allowed.

References

Cockcroft and Gault 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

Doolan et al 1962
Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 1962; 32:65.

Appendix I Country-Specific Requirements

Country	Country-specific requirements
France	**Local CSP/addendum version**: Version 1.0 dated 28 Apr 2022 New/revised text in *Italic and underline* **Section of protocol affected**: Section 1.1 Synopsis – Number of participants **Change:** Approximately 351 patients with histologically or cytologically documented EGFRm (Ex19del and/or L858R) NSCLC with resectable (clinical stage II to IIIB) disease will be randomized in a 1:1:1 ratio to receive investigators choice of platinum-based chemotherapy plus placebo or osimertinib, or osimertinib alone. *During the feasibility, the sites announced that they were monitoring between 30 and 70 patients/year with resectable stage II-IIB N2 non-small cell lung cancer. However, among this population, patients with an EGFR gene mutation represent a small proportion, around 10%. We consider a screening failure rate of around 80%.* *Taking into account all the study criteria, including EGFR mutation status, the sites undertake to include between 1 and 2 patients by the end of the recruitment period planned in October 2023 (i.e. approximately 55 screenings and 11 randomisations in total expected over this period in France).* **Section of protocol affected**: Section 4.1 Overall design **Change:** Approximately 351 patients with histologically or cytologically documented EGFRm (Ex19del and/or L858R) NSCLC with resectable (clinical stage II to IIIB) disease will be randomized 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 mainland China], and Chinese living in mainland China), and mutation type (Ex19del versus L858R). *EGFR mutation status is known to differ in the Asian and non- Asian populations (Zhang et al 2016). Asian race has been found to be a prognostic factor for survival and response to chemotherapy in NSCLC (Soo et al 2012). The median age of diagnosis in Asian patients with lung cancer is younger than Caucasian patients, particularly among never-smokers, which is the typical population that harbors that EGFR mutation driven lung cancers. Hence, several peer reviewed publications have recommended that "The ethnic differences in epidemiology and clinical behaviors should be taken into account when conducting global clinical trials that include different ethnic populations" (Zhou 2011). Therefore to account for any potential impact of race on treatment response in this population, participants will be stratified at randomization by race (Chinese Asian; non-Chinese Asian; non-Asian), with a specific stratum of Chinese Asian for the purposes of reporting in China in the NeoADAURA study.*

	Section of protocol affected: Section 5.1 Inclusion criteria - Criterion #9 **Change:** Life expectancy > 6 months prior to randomization. *The investigator should make a holistic assessment of the patient's status to determine if there are any medical concerns that would affect the life expectancy. The definition of 6 months is used to define the hospice population that was considered to be terminally ill and have only 6 months or less to live. The NeoADAURA is studying the NSCLC population that is considered curable rather than terminally ill because the treatment (including surgery) is done for curative intent rather than for terminally ill patients with less than 6 months to live.* **Section of protocol affected**: Section 5.1 Inclusion criteria - Criterion #4 **Change:** Male or female, at least 18 years of age. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative. *Age in itself is not a relevant variable in predicting whether a patient will benefit from the study treatments. As per some results presented in the investigator Brochure, age has no impact on the pharmacokinetics of Osimertinib.* **Section of protocol affected**: Section 5.1 Inclusion criteria - Criterion #1 **Change:** Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. *Need to be affiliated to a Social Security (Article L1121-8-1 of the Public Health Code). People legally protected according to the Public Health Code (articles L1121-5, -6, -7 and -8) will not be eligible to participate in this study.*
Germany	**Local CSP/addendum version**: Version 1 dated 02 Jul 2020 New/revised text in *Italic and underline.* **Section of protocol affected**: Section 1.3, Table 1: **Change:** Modification of Table entry for Pregnancy test at Treatment Discontinuation; added "*X*" **Section of protocol affected**: Section 8.3.2: **Change:** Updated wording in two sentences to reflect an additional pregnancy test at the treatment discontinuation visit: 1st change: modified wording: "Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug, ~~and then~~ Q3W prior to study treatment administration on the first day of each treatment cycle *and at the treatment discontinuation visit.*"

	2nd change: additional sentence: *"Pregnancy tests can be performed at any other time during study treatment in accordance with local clinical practice."* **Section of protocol affected**: Appendix A; Section A3: Informed Consent **Change:** Updated wording: Deleted the referral to a legal representative from three sentences: 1st deletion: *"The Investigator or his/her representative will explain the nature of the study to the patient ~~or his/her legally authorized representative~~ and answer all questions regarding the study."* 2nd deletion: *"Participants ~~or their legally authorised representative~~ will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre."* 3rd deletion: *"A copy of the ICF(s) must be provided to the participant ~~or the participant's legally authorised representative~~."* **Local CSP/addendum version**: Version 3 dated 31 May 2022 New/revised text in *Italic and underline.* **Sections of protocol affected**: • Table 1 footnote y was amended: This assessment may be performed outside of the 28-day screening period (see Footnote g). Patients are eligible to be considered for inclusion in the study if they have tumours that 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, Exon 20 insertions, S7681 and L861Q), as detected by the cobas® EGFR Mutation Test v2 in tumour tissue sample by prospective testing in central/ *local* lab. Enrolment based on a pre-existing EGFR-mutation positive tissue test result using the cobas® EGFR Mutation Test v2 or FoundationOne® CDx is also allowed, and tumour tissue sample should be provided (where available) for retrospective testing using cobas® EGFR Mutation Test v2 in central lab (EGFR mutation status result not needed to proceed with patient randomization in these cases) *Enrolment based on a local prospective EGFR-mutation positive tissue test result using the cobas® EGFR Mutation Test v2 is allowed, and tumour tissue sample must be provided for retrospective testing using cobas® EGFR Mutation Test v2 in central lab after*

local positive result is received (central EGFR mutation result is not needed to proceed with patient randomisation in these cases). Any remaining tissue and DNA extracts following completion of central cobas testing may be used for diagnostic development and exploratory biomarker testing, including NGS. Additional testing is not applicable in China. See Section 8.7.1.1 for further details.

- Section 5.4 - Local EGFR mutation analysis was added:

  Individuals who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened, with the exception of patients with a central/*local* EGFR test negative result for Ex19del or L858R.

- Table 16 - local EGFR mutation analysis was added in main column:

Table 16 Mandatory samples and timepoints for biomarker analysis

	Sample type *(analysis purpose)*					
	Tumour FFPE tissue	**Remaining tumour FFPE tissue**	**Plasma**	**Whole blood**	**Surgical tumour FFPE tissue**	**Notes**
Timepoint	*(central/local EGFR mutation analysis)*	*(exploratory analysis)*	*(central EGFR mutation analysis, MRD, ctDNA testing)*	*(CHIP & HLA analysis)*	*(MPR & exploratory analysis)*	

- Section 8.5.1 - SAE reporting via FAX/ Email was added/specified:

  If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone *(FAX-transmission) or via Email*. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

- Section 8.7.1.1 - Specification added: *(iii) prospective local tumour tissue analysis of EGFR mutation status performed using the cobas® EGFR Mutation Test v2*;

- Section 8.7.1.1 - Specification added:

  For patients entering the study based upon a local prospective test result, the local prospective EGFR laboratory results and the test method used should be collected and maintained as a source document and captured in the eCRF.

  These patients whose prospective local EGFR results are positive must provide FFPE tumour tissue for retrospective testing with the cobas® EGFR Mutation Test v2 in a central laboratory after local positive result is received (central EGFR mutation result is not needed to proceed with patient randomisation in these cases).

  Local prospective cobas® EGFR Mutation Test v2 tumour tissue analysis should be performed in a licensed, CLIA-certified or locally accredited clinical laboratory according to local standard procedures. Only the required amount of tumor tissue should be sent for prospective local EGFR testing. The Local lab will return any remaining tissue including stained and unstained slides to the site. If this cannot be done all remaining tissue, together with leftover extracted DNA must be destroyed at the local lab when the test is completed.

Service agreements with local laboratories must state that tissue cannot be used for the purposes other than contracted cobas® EGFR Mutation Test v2

Local CSP/addendum version: Version 5 dated 20 Jul 2023

New/revised text in *Italic and underline*

Section of protocol affected:

Table1. footer: The following text has been deleted:

~~*FNA, Fine needle aspirate*~~

Table1 footer: The following text has been deleted:

~~*In the case that neither tumour tissue sample with preserved tumour tissue architecture, nor pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx EGFR test result per IFU from a tumour sample is available, EGFR mutation status can be centrally confirmed, when permitted by AstraZeneca, in a tumour FFPE FNA sample, collected per SoC prior to, or during, screening, using the Idylla™ EGFR Mutation Test. Provision of additional tumour FFPE FNA samples, if available, is requested for future confirmation testing using an FDA approved FNA test. The total number of tumour FFPE FNA slides required can be found in the Laboratory Manual. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment. Any remaining tumour samples and DNA extracts following completion of central EGFR testing may be used for diagnostic development and exploratory biomarker testing, including NGS. See Section 8.7.1.1 for further details.*~~

Section 4.1.1: The following text has been deleted:

~~*tumour tissue or FNA sample) is also permitted or fine needle aspirate [FNA] sample[1] [1] An archived tissue or new biopsy specimen, when no archived tissue is available, is acceptable. Patients will only undergo tumour biopsy if it is considered a medically acceptable risk by the investigator. When archival or new FFPE tumour tissue biopsy is not available, FFPE FNA sample collected per SoC prior to or during screening is also acceptable.*~~

Section 4.1.1: The following text has been deleted:

~~*In the case that neither tumour tissue sample with preserved tumour tissue architecture, nor pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx EGFR test result per IFU from a tumour sample is available, EGFR mutation status can be centrally confirmed, when permitted by AstraZeneca, in a tumour FFPE FNA sample collected per SoC prior to, or during, screening, using the Idylla™ EGFR Mutation Test. Provision of additional tumour FFPE FNA samples, if available, is requested for future confirmation testing using an FDA approved FNA test. The total number of tumour FFPE FNA slides required can be found in the Laboratory Manual. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment,*~~

	~~*and participants who are EGFR mutation negative or do not meet eligibility criteria must not be randomised into the study*~~ Section 6.3.1: The following text has been deleted: ~~*In the case that neither tumour tissue sample with preserved tumour tissue architecture, nor pre-existing cobas® EGFR Mutation Test v2 or FoundationOne® CDx EGFR test result per IFU from tumour sample is available, a tumour FFPE FNA sample collected per SoC prior to, or during, screening is acceptable for central EGFR mutation status confirmation using Idylla™ EGFR Mutation Test, when permitted by AstraZeneca. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment.*~~ Section 8.7.1.1: The following text has been deleted: ~~*or (iii) in the case that neither tumour tissue sample with preserved tumour tissue architecture nor pre-existing cobas® EGFR Mutation Test v2, nor FoundationOne® CDx EGFR test result from tumour sample per IFU is available, EGFR mutation status can be centrally confirmed, when permitted by AstraZeneca, in a tumour FFPE FNA sample, collected per SoC prior to, or during, screening, using the Idylla™ EGFR Mutation Test. Note: A pre-existing EGFR test result obtained via a local Idylla™ EGFR Mutation Test is not permitted for patient enrolment.*~~ Section 8.7.1.1: The following text has been deleted: ~~*For patients who are enrolled based on tumour FFPE FNA samples, provision of additional tumour FFPE FNA samples, if available, is requested for future confirmation testing using an FDA approved FNA test. The total number of tumour FFPE FNA samples required can be found in the Laboratory Manual.*~~ ~~*or tumour FFPE FNA block*~~ Section 8.7.1.1: The following text has been deleted: ~~*If such a biopsy sample is not available, tumour FFPE FNA samples, if available, are acceptable for central laboratory testing by the Idylla™ EGFR Mutation Test, when permitted by AstraZeneca.*~~

Appendix J Abbreviations

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AxMP	Auxiliary medicinal product
BCRP	Breast Cancer Resistance Protein
BICR	Blinded independent central review
BM	Bronchial margin
CHIP	Clonal haematopoiesis of indeterminate potential
C	Cycle
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
ClinRO	Clinician reported outcome
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COA	Clinical outcome assessment
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract Research Organisation
CRT	Concurrent chemoradiation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
D	Day
DCO	Data cut-off date

Abbreviation or special term	Explanation
DES	Data Entry Site
DFS	Disease free survival
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
EBUS	Endobronchial ultrasound
EDC	Electronic data capture
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic case report form
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor-tyrosine kinase inhibitor sensitising mutation, including exon 19 deletions and point mutations in exon 21 (L858R, L861Q) and exon 18 (G719X)
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
EORTC	European Organisation for Research and Treatment of Cancer
EM	Erythema multiforme
ePRO	Electronic tablet (for patient reported outcomes)
ESMO	European Society for Medical Oncology
EU CTR	European Union Clinical Trials Regulation
EUS	Oesophageal ultrasonography
Ex19del	Exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain
FAS	Full analysis set
^{18}FDG-PET	18F-fluorodeoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second
FFPE	Formalin fixed and paraffin embedded
FNA	Fine needle aspirate
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony stimulating factors
GC	Gemcitabine/carboplatin
GCF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
Hb	Haemoglobin
HIV	Human immunodeficiency virus

Abbreviation or special term	Explanation
HLA	Human leukocyte antigen
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQoL	Health-related Quality of Life
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	Instructions for use
IgG	Immunoglobulin G
IO	Immuno-oncology
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International normalised ratio
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-uterine Device
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan-Meier
L858R	Sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LFT	Liver function test
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MDT	Multi-disciplinary team
MPR	Major pathological response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
MUGA	Multi-gated acquisition (scan)
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-generation sequencing
NIMP	Non-investigational medicinal product
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
ObsRO	Observer reported outcome
ORR	Objective response rate
OS	Overall survival
PA	Pulmonary artery
P-gp	P-glycoprotein
pCR	Pathological complete response
PERCIST	PET Response Criteria in Solid Tumours
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PS	Performance status
PV	Pulmonary vein
QD	Once daily
Q3W	Every three weeks
QoL	Quality of life
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RCRI	Recalibrated revised cardiac risk index
RTSM	Randomisation and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SJS	Stevens-Johnson syndrome
SoA	Schedule of activities

Abbreviation or special term	Explanation
SoC	Standard of care
SND	Systematic node dissection
SUSAR	Suspected unexpected serious adverse reactions
T790M	EGFR mutation resulting in substitution of threonine with methionine at amino acid position 790 in exon 20 of EGFR
TdP	Torsades de Pointes
TEN	Toxic epidermal necrolysis
TKI	Tyrosine kinase inhibitor
TNM	Tumour-Node-Metastasis
ULN	Upper limit of normal
US	United States
VATS	Video assisted thoracoscopic surgery
WHO	World Health Organisation
WoCBP	Women of Childbearing Potential

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Document Name: d516ac00001-csp-v5		
Document Title:	D516AC00001 Clinical Study Protocol version 5	
Document ID:	Doc ID-004187902	
Version Label:	7.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
13-Dec-2023 12:15 UTC	PPD	Qualified Person Approval
13-Dec-2023 16:49 UTC	PPD	Content Approval
13-Dec-2023 10:00 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.