Clinical Study Protocol	
Drug Substance	Osimertinib
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A Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of osimertinib as maintenance therapy in patients with locally advanced, unresectable EGFR mutation-positive Non-Small Cell Lung Cancer (Stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy (LAURA)

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VERSION HISTORY

Version 1, 23 March 2018
Initial Creation

Version 2, 28 February 2020 Changes to the protocol are summarized below:
The primary change in this protocol is: • To add that before the PFS analysis, patients may receive open-label osimertinib after BICR-confirmed disease progression. After the PFS analysis, patients may receive open-label osimertinib after investigator-assessed disease progression. In addition, changes have been made to update the protocol with the current data from the osimertinib development programme. The primary, secondary and exploratory objectives of this protocol remain unchanged. Major changes to the protocol are summarized below: **Section 1.1 (Schedule of Activities), Section 1.2 (Synopsis), Section 1.3 (Schema), Section 4.1 (Overall Design), Section 7.2 (Treatment with open-label osimertinib), Section 7.5 (Patient management post-primary PFS analysis)**: Added that patients may receive open-label osimertinib after BICR-confirmed disease progression. Patients must not receive any other anti-cancer therapies between discontinuation of study treatment and start of open-label osimertinib. **Section 1.1 (Schedule of Activities) and Section 8.3.2 (Time period and frequency for collecting AE and SAE information):** Increased duration of AESI monitoring during progression and survival follow-up. **Section 1.2 (Synopsis), Section 2.3 (Study rationale)**: Data from the data-cut off 2 of the FLAURA study were added. **Section 2.5.4 (Overall benefit/risk)**: The frequency of ILD and ILD-like ADRs was added, including the frequency of fatal events. **Section 5.1 (Inclusion criteria):** It was added that patients with a stage III tumor of squamous histology who have a pre-existing local positive test result (Ex19del or L858R) are eligible for Part I screening. Also clarified the tumor tissue specimen required for entry into Part I screening.

Section 5.2 (Exclusion criteria): Text was added to clarify that patients are eligible in Part I of the study if none of the Part II screening exclusion criteria 1, 2, 7, 9-11, and 15-20 apply. The exclusion criterion relating to risk of QTc prolongation was also updated, with further definition of electrolyte abnormalities and medical history. In addition, minor changes were made to exclusion criteria 6, 8, 10, and 13.

Section 5.3.2 (Blood donation): Patients may not donate blood from date of randomization until 28 days after the last dose of study treatment.

Section 6.1.1 (Investigational products): Supply of open-label osimertinib was added.

Section 6.6 (Dose modification), Section 8.4.4.1 (QTc prolongation): Procedures for handling dose interruptions for patients with QTc prolongation were updated to match current recommendations. Guidance for correction of electrolyte levels before first dose was also added.

Section 8.4.4.4 (Erythema multiforme and Stevens-Johnson syndrome): Management of patients with signs and symptoms of erythema multiforme or Stevens-Johnson syndrome were added, following updates to the osimertinib prescribing information.

Section 9.4.1.1 (Primary analysis of PFS), Section 9.4.2.2 (Analysis of overall survival), Section 9.4.2.3 (Analysis of objective response rate), Section 9.4.2.4 (Analysis of Duration of Response): Definitions of these endpoints were added.

Section 9.4.2.10 (Analysis of post-progression outcomes): The definition of time to first and time to second subsequent therapies or death were changed to match the statistical analysis plan.

Section 9.6 (China Cohort): It was added that analysis of the China cohort will take place after analysis of the Global cohort.

CSP Version 3.0, 03 February 2021
Changes to the protocol are summarized below:

The primary changes in this protocol are:

- To enable the use of the FoundationOne® CDx test for local EGFR mutation status testing
- To clarify the PRO data collection schedule
- To provide further clarification on the timing of when patients may receive open-label osimertinib, and the supply of open-label osimertinib after the final OS analysis.
- To provide further clarification on various inclusion and exclusion criteria concerning patient disease characteristics, concurrent chemoradiation (CCRT), electrolyte correction, eligibility for participants with a resolved or chronic hepatitis B virus (HBV) infection, and other study participation

- To provide further clarification on the timing of adverse events (AE), serious adverse events (SAE), and adverse events of special interest (AESI) collection.

The primary, secondary and exploratory objectives of this protocol remain unchanged. The above and other additional changes are described in detail below. Minor editorial changes have also been made, however these are not included in the summary below.

Section 1.1 (Schedule of assessments [Table 1]):

- Adverse event and concomitant medication data collection added at Screening Part I to clarify AE/SAEs are to be collected from signature of the first ICF.
- **Table and Footnote (e):** Clarified that either archival or newly acquired tumor tissue samples can be provided for prospective and retrospective central EGFR mutation analysis. This change was also reflected throughout the CSP.
- **Footnote (f)**: The FoundationOne® CDx test was included as a FDA-approved tissue-based CDx for EGFR mutation status. Language amended to clarify that tissue is to be provided for retrospective testing only for patients that did not undergo Part 1 screening.
- **Footnote (l):** Clarified that the collection of the plasma sample for PK can be omitted if the patient did not have exposure to IP for at least 7 days prior to the visit.
- **Footnote (n):** Clarification of the timings given for collection of PROs at treatment discontinuation following BICR-confirmed disease progression are relative to the date of the treatment discontinuation visit; and for patients who discontinue prior to BICR-progression the timings of collection of PROs are relative to the disease progression visit.

Section 1.2 (Synopsis): Updated in line with changes made throughout the CSP.

Section 4.1 (Overall design):

- Correction made to the number of patients needing to be screened, changed to 1333 patients.
- Clarified that recruitment will continue in mainland China until at least 40 patients have been randomized.
- Text added to clarify that relevant local EGFR mutation-positive test results are those obtained using a tissue-based FDA-approved CDx for TAGRISSO (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test).
- Text added to describe when study blind will be broken, and also when cessation of AstraZeneca supplied open-label osimertinib will occur.
- Clarified that either archival or newly acquired tumor tissue samples can be provided for prospective and retrospective central EGFR mutation analysis.

Section 5.1.1 (Part I Screening, Inclusion Criteria): Text added to clarify that relevant local EGFR test results are those obtained using a tissue-based FDA-approved CDx for TAGRISSO (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use.

Section 5.1.2 (Part II Screening, Inclusion criteria): Text added to clarify that relevant local EGFR test results are those obtained using a tissue-based FDA-approved CDx for TAGRISSO (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use.

Section 5.1.2 (Part II Screening, Inclusion criterion 5): The following clarification text was added: *Patients with a stage III tumor of squamous histology who have a pre-existing local positive test result (Ex19del or L858R), irrespective of EGFR test used or lab accreditation, and confirmed by central testing during Part I screening, are eligible for Part II screening.

Section 5.1.2 (Part II Screening, Inclusion criterion 6): Text added to clarify that relevant local EGFR test results are those obtained using a tissue-based FDA-approved CDx for TAGRISSO (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test).

Section 5.1.2 (Part II Screening, Inclusion criterion 8): Clarified final chemotherapy administration must be completed prior to, or concurrently with, the final dose of radiation. Reference to platinum and pemetrexed doublet therapy removed and changed to a final cycle of chemotherapy is permitted up to 7 days after the last dose of radiation, if at least 2 cycles have already been given concurrently.

Section 5.2.2 (Part II Screening, Exclusion Criterion 5): Text added to specify correction of electrolyte abnormalities to within normal ranges can be performed during the screening period.

Section 5.2.2 (Part II Screening, Exclusion Criterion 8): Updated eligibility for participants with a resolved or chronic HBV infection.

Section 5.2.2 (Part II Screening, Exclusion criterion 14): Text amended to clarify that patients are excluded if a participant in another clinical study with an IP administered in the previous 4 weeks prior to randomization.

Section 5.3.1 (Pregnancy) and Appendix J: Text amended to specify a 'highly effective' contraceptive measure must be used in female patients of child-bearing potential.

Section 5.3.3 (Chronic hepatitis B): New section added outlining recommendations for the management of patients with chronic HBV infection.

Section 6.6 (Dose modification, Table 5): Text amended to clarify that dose modifications are only permitted for adverse reactions. In addition, the timing of recovery and permanent study treatment withdrawal for patients with QTc prolongations were clarified as relative to study drug interruption, and additional clarification text regarding restart dose was added.

Section 6.7 (Treatment after the end of the study): Text amended to describe when cessation of AstraZeneca supplied open-label osimertinib will occur, and further options for drug supply.

Section 7.1.1.2 (Survival follow-up): Text moved from Section 7.1.1.2.2 (Post primary PFS analysis) to this section, since survival follow-up of patients is applicable prior to and post primary PFS analysis.

Section 7.1.1.2.1 (Prior to primary PFS analysis): Text added to clarify that follow-up for completion of ePROs are relative to the date of the treatment discontinuation visit. In addition, text was added to clarify that both SAEs and AESIs are collected only if considered related to prior study treatment, or open-label osimertinib.

Section 7.1.1.2.2 (Post primary PFS analysis): Text added to clarify that follow-up for completion of ePROs are relative to the date of the treatment discontinuation visit.

Section 7.2 (Treatment with open-label osimertinib): Text amended to clarify when treatment assignment may be unblinded and when the patient may receive open-label osimertinib. In addition, text added to advise the investigator should monitor the patient per local clinical guidance during open-label treatment with osimertinib.

Section 7.6 (Patient management post-final OS analysis): AESIs added to the list of information collected during treatment and for 28 days after last dose. In addition, AESI added to be reported following discontinuation of study treatment (plus 28-day follow-up) when considered causally related to osimertinib. Text added to describe when cessation of AstraZeneca supplied open-label osimertinib will occur.

Section 8.1.1 (RECIST v1.1) and Section 8.1.2 (Screening tumor sample for EGFR mutation analysis), including all subsections: Sections 8.1.1 and 8.1.2 were re-ordered for logical flow, in order to appear in the sequence in which the assessments are to be performed during the study.

Section 8.1.1.1.1 (Patients without a positive local tissue-based EGFR mutation test result): Previously Section 8.2.1.1.1. Title simplified. Instructions relating to the provision of tumor tissue revised (from a minimum of 8 sections to preferably 12 [except in China]), and reference to the Laboratory Manual for further details added. Clarified that either archival or newly acquired tumor tissue samples can be provided for central EGFR mutation analysis.

Section 8.1.1.1.2 (Patients with a positive local tissue-based EGFR mutation test result): Previously Section 8.2.1.1.2. Title simplified. Local cobas® EGFR Mutation Test v2 changed to local EGFR test, in line with early changes. Clarified that either archival or newly acquired tumor tissue samples can be provided for central EGFR mutation analysis.

Section 8.1.1.2 (Plasma samples for EGFR mutation testing): Previously Section 8.2.1.2. China specific requirement for blood volume added.

Section 8.1.3 (Clinical outcome assessments): Text added to clarify the timing of PRO collection for patients who discontinue study treatment prior to BICR-confirmed progression.

Section 8.2.1 (Clinical safety laboratory assessments, Table 6): Footnote (c) added to clarify either dipstick and local lab testing are acceptable methods of urinalysis and results to be reported as qualitative outcomes.

Section 8.2.4 (Vital signs): Added option of taking measures in a sitting position if supine not feasible.

Section 8.3.2 (Time period and frequency for collecting AE and SAE information): Text amended to clarify AE/SAEs to be collected from signature of the first ICF. Table 8 amended to clarify when and which SAEs and AESIs need to be collected during each follow-up stage of the study. Footnote (a) added to note additional safety assessments maybe performed in line with local clinical practice post final OS analysis but not collected as part of the study data capture.

Section 8.3.7 (Adverse events based on examinations and tests): Additional reason of 'considered clinically relevant as judged by the investigator' added to the list of reasons to report a laboratory value or vital signs as an AE**.**

Section 8.4.4.1 (General dose adjustments for adverse events): Text amended to clarify that dose interruptions are only permitted for adverse reactions (related to osimertinib/matching placebo). In addition, the timing of recovery and permanent study treatment withdrawal, for patients with toxicities, were clarified as relative to study drug interruption.

Section 8.4.4.3 (QTc prolongation): The timing of recovery and permanent study treatment withdrawal, for patients with toxicities, were clarified as relative to study drug interruption.

Section 8.5 (Pharmacokinetics): Text added to describe when collection of the plasma sample for PK can be omitted.

Section 8.5.2 (Storage and destruction of pharmacokinetic samples): Timing of destruction of all PK samples and residual samples added as maximally 12 months post final CSR.

Section 8.8.3 (Storage, re-use and destruction of biomarker samples): Text added to describe the requirement in China for mutation testing residual plasma and tissue samples to be destroyed or repatriated maximally 5 years after study indication approval for marketing in China.

Section 9.2 (Sample size determination): Clarified that recruitment will continue in mainland China until at least 40 patients have been randomized.

Section 9.3.3 (Pharmacokinetic Analysis Set): Definition of the PK Analysis Set revised for consistency with the SAP.

Section 9.4.1.1.1 (Primary analysis of PFS): Details of strata collapse strategy removed and a cross-reference to the SAP added for further details.

Section 9.4.1.1.3 (Subgroup analyses): Revised details of results to be presented for subgroup analyses in line with the SAP.

Section 9.4.1.2.2 (Analysis of overall survival): Text added to clarify the sufficient number of events is ≥ 20 deaths across both treatment groups with at least 5 events per arm.

Section 9.4.1.2.4 (Analysis of Duration of Response): Removed reference to Expected Duration of Response analysis, in line with the SAP.

Section 9.4.1.3.6 (Comparison of baseline tumor EGFR mutation status): Text added to describe the analysis method to be used to compare baseline tumor EGFR mutation status between local and central tests.

Section 9.6 (China Cohort): Clarified that recruitment will continue in mainland China until at least 40 patients have been randomized. Reference to a separate Asia population analysis removed.

Appendix C (Handling of Human Biological Samples): Text added to describe the requirement in China for mutation testing residual tissue and plasma samples to be destroyed or repatriated maximally 5 years after study indication approval for marketing in China, and timing of destruction of all PK samples and residual samples collected in China added as maximally 12 months post final CSR.

CSP Version 4.0, 25 February 2022
Changes to the protocol are summarized below:

The primary changes in this protocol are:

- To clarify the number of patients planned to be recruited in China.
- To remove the requirement for the collection of PROs after the primary PFS analysis.
- To clarify the nature and timing of AE data collection in relation to the Screening Part I and Screening Part II study periods.

The primary, secondary and exploratory objectives of this protocol remain unchanged. The above and other additional changes are described in detail below. Minor editorial changes have also been made; however, these are not included in the summary below.

Section 1.1 (Schedule of assessments [Table 1]): Footnote (n) was revised to state that PROs will no longer be collected for any patient after the primary PFS analysis. New footnote (aa) added to clarify that only AEs and SAEs related to study procedures will be collected during Screening Part I.

Section 1.2 (Synopsis): Updated in line with changes made throughout the CSP.

Section 4.1 (Overall design): Updated in line with changes made throughout the CSP.

Section 7.1.1.2.2 (Post primary PFS analysis) and Section 8.1.3 (Clinical outcome assessments): The requirement for the collection of PRO data after the primary analysis has been removed.

Section 7.5 (Patient management post primary PFS analysis and up to final OS analysis): Text clarified to state study assessments will continue per the SoA following the primary PFS analysis for all patients still on study treatment.

Section 8.1.3 (Clinical outcome assessments): Text revised to note that PRO data will no longer be collected for any patient after the primary PFS analysis. Text clarifying the timing of PRO collection for patients who discontinue study treatment prior to BICR-confirmed progression was removed.

Section 8.3.2 (Time period and frequency for collecting AE and SAE information): The types of AEs to be collected in the Part I Screening period has been clarified (all SAEs and AEs related to study procedures only) and details added to Table 8. Further details on AE collection from the time of signing the Part II Screening ICF until the 28-day follow-up visit has been added to the text.

Section 9.2 (Sample size determination) and Section 9.6 (China cohort): Text revised to state that 200 patients will be "randomized" (change from "recruited") and approximately 30 to 40 patients are planned to be recruited in China. The requirements for these patients to be recruited from mainland China was also removed.

Section 9.3.1 (Full Analysis Set), Section 9.3.2 (Safety Analysis Set), and Section 9.6 (China Cohort): Text revised to remove statement that any patients recruited in China, after global recruitment has ended, will not be included in the FAS and SAF. The FAS will include all randomized patients, and the SAF will include all randomized patients who received at least one dose of study treatment. Analysis of PFS and OS in the China cohort will be conducted at the same time as for the overall population.

Section 9.4.1.1.3 (Subgroup analyses): Patients enrolled at a Chinese site and declaring themselves of Chinese ethnicity vs patients enrolled at non-Chinese site or declaring themselves of non-Chinese ethnicity was added as a subgroup for analyses.

Section 9.4.1.2.11 (Analysis of EORTC QLQ-C30 and QLQ-LC13): Clarification added that PRO analyses will only take place at the time of the primary PFS analysis.

CSP Version 5.0, 03 November 2023 Changes to the protocol are summarized below:
The primary changes in this protocol are: • To update the MTP to increase the chance of formally testing OS by changing the hierarchy to PFS, OS, and then CNS PFS ensuring OS is tested prior to CNS PFS. The primary, secondary, and exploratory objectives of this protocol remain unchanged. The above and other additional changes are described in detail below. Minor editorial changes have also been made; however, these are not included in the summary below. Throughout: Updates made to MTP; applies to **Synopsis**, **Section 9.1**, **Section 9.2**, **Section 9.4.1.2.1**, and **Section 9.4.2.2**. The MTP has been updated to change the hierarchy to PFS, OS, and then CNS PFS, so that OS is tested prior to CNS PFS. With the changing importance of an OS benefit for EGFRm NSCLC, this increases the chance of formally testing OS. Throughout: Updates made to align with the latest PSSR (v28); applies to **Section 6.5.1**, **Section 6.6**, **Section 8.4.2.2**, **Section 8.4.4.6, and Appendix I**. **Section 8.4.4.7** added. Throughout: Updates made to include mandatory text from the recently released Late Development Oncology CSP Template (based on the AstraZeneca CSP TransCelerate Template TMP-0010225) and to harmonize the content to meet the EU CTR requirements; applies to **Section 4.4**, **Section 6.7**, **Section 7.6, Section 8.4.5**, **Appendix A**, and **Appendix B**.

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 Schedule of Activities (SoA) up to Primary PFS Analysis

Table 1 Study Assessments

	Screening		Treatment Period									Follow-up Period			Details in CSP section
Visit (V) Name	**Screening Part I**	**Screening Part II/V1**	**Random-ization/ V2**	**V3**	**V4**	**V5**	**V6**	**V7-9 [a]**	**V10-11 [a]**	**V12+ [a]**	**Treatment Discont-inuation**	**28-day Follow-up [b]**	**Progression Follow-up [c]**	**Survival Follow-up**	
Week	**NA**	**NA**	**1**	**2**	**4**	**8**	**12**	**16-24**	**32-40**	**48+**	**NA**	**NA**	**NA**	**NA**	
Day	**NA**	**-28 to 0**	**1**	**15**	**29**	**57**	**85**	**113-169**	**225-281**	**337+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**NA**	**NA**	**±2**	**±2**	**±3**	**±3**	**±3**	**±7**	**± 7**	**+ 7**	**+ 7**	**± 7**	**± 7**	
Written informed consent for Part I Screening	X														Section 5.1
Written informed consent for Part II Screening [d]		X													Section 5.1 and 5.2
Diagnostic clinical procedures															
Tumor sample (archival or newly acquired) for prospective central EGFR mutation analysis [e]	X														Section 5.1 and Section 8.1.1
Tumor sample (archival or newly acquired) for retrospective central EGFR mutation analysis		X [f]													Section 5.1 and Section 8.1.1

Table 1 Study Assessments

	Screening		Treatment Period									Follow-up Period			Details in CSP section
Visit (V) Name	**Screening Part I**	**Screening Part II/V1**	**Random-ization/ V2**	**V3**	**V4**	**V5**	**V6**	**V7-9 [a]**	**V10-11 [a]**	**V12+ [a]**	**Treatment Discont-inuation**	**28-day Follow-up [b]**	**Progression Follow-up [c]**	**Survival Follow-up**	
Week	**NA**	**NA**	**1**	**2**	**4**	**8**	**12**	**16-24**	**32-40**	**48+**	**NA**	**NA**	**NA**	**NA**	
Day	**NA**	**-28 to 0**	**1**	**15**	**29**	**57**	**85**	**113-169**	**225-281**	**337+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**NA**	**NA**	**±2**	**±2**	**±3**	**±3**	**±3**	**±7**	**± 7**	**+ 7**	**+ 7**	**± 7**	**± 7**	
Plasma sample for retrospective central EGFR mutation testing		X													Section 8.1.1
Routine clinical procedure															
Demography & baseline characteristics [u]	X	X													Section 5.1
Medical/surgical history	X	X													Section 5.1
Inclusion/exclusion	X	X	X												Section 5.1 and 5.2
Physical examination including weight [g]		X	X (pre-dose)	X	X	X	X	X	X	X	X				Section 8.2.3
Height		X													Section 8.2.3
WHO performance status		X	X (pre-dose)	X	X	X	X	X	X	X	X		X		Section 8.2.7
Vital signs [g]		X	X (pre-dose)	X	X	X	X	X	X	X	X				Section 8.2.4
Digital ECG [h]		X	X (pre-dose)	X	X	X	X	X	X	X	X	X[h]			Section 8.2.5
Echocardiogram/ MUGA (for LVEF)		X		every 12 weeks relative to randomization (±7 days) including week 36 (±7 days) [i]							X[i]				Section 8.2.6
Concomitant medication	X	X	At every visit and may be conducted by phone at 28-day follow-up												Section 6.5
Anti-cancer and surgical treatment		X											X	X	Section 7.1.1.1 and 7.1.1.2

Table 1 Study Assessments

	Screening		Treatment Period									Follow-up Period			Details in CSP section
Visit (V) Name	**Screening Part I**	**Screening Part II/V1**	**Random-ization/ V2**	**V3**	**V4**	**V5**	**V6**	**V7-9 [a]**	**V10-11 [a]**	**V12+ [a]**	**Treatment Discont-inuation**	**28-day Follow-up [b]**	**Progression Follow-up [c]**	**Survival Follow-up**	
Week	**NA**	**NA**	**1**	**2**	**4**	**8**	**12**	**16-24**	**32-40**	**48+**	**NA**	**NA**	**NA**	**NA**	
Day	**NA**	**-28 to 0**	**1**	**15**	**29**	**57**	**85**	**113-169**	**225-281**	**337+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**NA**	**NA**	**±2**	**±2**	**±3**	**±3**	**±3**	**±7**	**± 7**	**+ 7**	**+ 7**	**± 7**	**± 7**	
Routine safety measurements															
Adverse events	X[aa]	X	At every visit and may be conducted by phone at 28-day follow-up										X[c, x]	X[x]	Section 8.3
Pregnancy test [j]		X													Section 8.2.2
Safety laboratory assessments (clinical chemistry, hematology and urinalysis)[g]		X	X (pre-dose)	X	X	X	X	X	X	X	X				Section 8.2.1
Biomarker analyses															
Tumor sample upon disease progression (optional)[t]											at progression		at progression		Section 8.8
Plasma sample for ctDNA and blood borne biomarkers [t]		X	X (pre-dose)	X	X	X	X	X	X	X	X		X[k]		Section 8.8
Pharmacokinetic measurements															
Pre-dose blood sample (including metabolites)[l]					X		X	X (Day 169/ Week 24 only)							Section 8.5
Other assessments															
EORTC QLQ-LC13[m, n]			X (pre-dose)	Weekly up to week 8, thereafter every 4 weeks (±3 days) relative to randomization							X		X	X	Section 8.1.3.2
EORTC QLQ-C30[m, n]			X (pre-dose)	Week 4, week 8 and thereafter every 8 weeks (±3 days) relative to randomization							X		X	X	Section 8.1.3.1
PGIS[m, n]			X (pre-dose)	Every 8 weeks (±3 days) relative to randomization							X		X	X	Section 8.1.3.3

Table 1 Study Assessments

	Screening		Treatment Period									Follow-up Period			Details in CSP section
Visit (V) Name	**Screening Part I**	**Screening Part II/V1**	**Random-ization/ V2**	**V3**	**V4**	**V5**	**V6**	**V7-9 [a]**	**V10-11 [a]**	**V12+ [a]**	**Treatment Discont-inuation**	**28-day Follow-up [b]**	**Progression Follow-up [c]**	**Survival Follow-up**	
Week	**NA**	**NA**	**1**	**2**	**4**	**8**	**12**	**16-24**	**32-40**	**48+**	**NA**	**NA**	**NA**	**NA**	
Day	**NA**	**-28 to 0**	**1**	**15**	**29**	**57**	**85**	**113-169**	**225-281**	**337+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**NA**	**NA**	**±2**	**±2**	**±3**	**±3**	**±3**	**±7**	**± 7**	**+ 7**	**+ 7**	**± 7**	**± 7**	
PRO-CTCAE[m, n]			X (pre-dose)	Weekly up to week 8, thereafter every 4 weeks (±3 days) relative to randomization							X		X	X	Section 8.1.3.4
EQ-5D-5L[m, n]			X (pre-dose)	Week 4, week 8 and thereafter every 8 weeks (±3 days) relative to randomization							X		X	X	Section 8.1.3.5
Health Resource Use Module			X (pre-dose)		X	X	X	X	X	X	X	X	X[w]	X[y]	Section 8.1.4
Efficacy measurements															
Tumor assessments - Body CT/MRI and brain MRI (RECIST v1.1)[o]		X[o] (Incl. planning scan)		Every 8 weeks (± 1 week) for the first 48 weeks and then change to every 12 weeks (relative to randomization) until BICR-confirmed PD[z]											Section 8.1.2 and Appendix F
Pharmacogenetic sampling (optional)															
Genetic consent and blood sample (optional)[p]		X													Section 8.7
Study treatment administration															
Randomization			X[v]												Section 6.3
Study treatment dispensed (daily dosing)			X[s]		X	X	X	X	X	X					Section 6.1
Survival follow up															
Subsequent response / progression data [q]														X	Section 7.1.1.2
Survival status [r]														X[x]	Section 7.1.1.2

AESI = adverse event of special interest; BICR = blinded independent central review; CDx = companion diagnostic; CSP = Clinical Study Protocol; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid;; ECG = electrocardiogram; ECHO = echocardiogram; EGFR = epidermal growth factor receptor; EORTC QLQ-C30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung

Cancer 13 items; ePRO = electronic patient reported outcome; EQ-5D-5L = EuroQoL 5-Dimension 5-Levels; HRU= Health Resource Use; FDA = Food and Drug Administration; IP = investigational product; IVRS/IWRS = interactive voice response system/interactive web response system; LVEF = Left Ventricular Ejection Fraction; MRI = magnetic resonance imaging; MUGA = Multigated Acquisition Scan; NA = not applicable; OS = overall survival; PFS = progression free survival; PGIS=Patients Global Impression of Severity; PRO = patient reported outcome; PRO-CTCAE = Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event approximately 17 items; PD = Progressive Disease; PK = pharmacokinetics; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; V = Visit; WHO = World Health Organization.

a. Patients to attend visits every 8 weeks from Visit 9/Week 24 until Visit 12/Week 48, then every 12 weeks afterwards until BICR-confirmed disease progression.
b. As a minimum, telephone contact should be made with the patient 28 days (+ 7 days) following the discontinuation of study drug.
c. Patients who discontinue study drug for reasons other than BICR-confirmed disease progression will continue RECIST 1.1 tumor assessments every 8 weeks (relative to the date of randomization) or every 12 weeks after week 48 until BICR-confirmed disease progression. At the same time points WHO performance status, plasma samples for ctDNA and blood borne markers and information on HRU and anti-cancer and surgical treatments will be collected. EORTC QLQ-LC13, EORTC QLQ-C30, PGIS, PRO-CTCAE, EQ-5D-5L questionnaires will continue to be carried out at the same frequency as the treatment period until BICR-confirmed disease progression. Both SAEs and AESIs considered related to study treatment and/or study procedures will be collected throughout progression follow-up. After the primary PFS analysis, patients who are in progression follow-up will move on to survival follow-up and have progression assessed in accordance with local clinical practice. Formal RECIST v 1.1 measurements, ePROs, HRU, WHO performance status, ctDNA and blood-borne biomarkers will no longer be collected.
d. Consent may be taken prior to 28-day window if required. Part II screening period of 28 days will then start with first study-related assessment.
e. Tissue block (archival or newly acquired) must not be older than 12 months or slides must not be older than 60 days.
f. Tissue (archival or newly acquired) to be provided (where available) only for retrospective testing patients that did not undergo Part I screening (i.e., in circumstances where an EGFR positive-result was already available, derived from a tissue-based FDA approved CDx for TAGRISSO [i.e., **cobas**® EGFR Mutation Test v2 or FoundationOne® CDx test]). Tissue block must not be older than 12 months or slides must not be older than 60 days. A retrospective central EGFR mutation status test result is not needed to proceed with patient randomization.
g. The assessments are to be completed pre-dose on visit day. If screening assessments have been performed within 7 days prior to starting study treatment, they do not have to be repeated at Visit 2 if the patient's condition has not changed.
h. All ECG data (with the exception of screening ECG if the central ECG machine is not available) will be collected digitally for central analysis at scheduled visits and in the event of any cardiac adverse event. A 28-day follow-up ECG will be required if an on treatment assessment showed clinically significant abnormalities at treatment discontinuation to confirm reversibility of the abnormality.
i. MUGA or ECHO will be performed at screening, every 12 weeks relative to the date of randomization, at study treatment discontinuation and as clinically required. If a patient has had a MUGA or echocardiogram performed within 4 weeks prior to treatment discontinuation, the discontinuation visit ECHO/MUGA scan is not required unless clinically indicated. Patient will return for ECHO/MUGA assessment at week 36 additionally to align the assessment frequency every 12 weeks.
j. Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be conducted in women of child-bearing potential only
k. If a patient discontinues study treatment prior to BICR-confirmed progression, samples should continue to be collected every 8 weeks until week 48 and every 12 weeks after week 48 (relative to the date of randomization) until BICR-confirmed progression.
l. Plasma PK sampling (2 mL each) will be performed at pre-dose on day 29 (visit 4/ week 4), day 85 (visit 6/week 12) and day 169 (visit 9/week 24). Pre-dose PK samples should be collected within 1 hr before the dose on the day of collection. The collection of the plasma sample for PK can be omitted if the patient did not have exposure to IP for at least 7 days prior to the visit.
m. ePRO (Electronic devices; LogPads) must be assigned to patients only on the day of randomization; baseline ePROs must be completed by patients prior to dosing, when they are still in the clinic on the day of randomization. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists. LogPads used for ePRO collection should be returned to site at the nearest visit as soon as the last assessment is completed by patient.
n. PROs to be collected at treatment discontinuation visit following BICR-confirmed disease progression and at week 8 (±3 days), week 16 (±3 days), and week 32 (±3 days) relative to the date of the treatment discontinuation visit. For patients who discontinue study treatment prior to BICR-confirmed progression, PROs should be collected at the study treatment discontinuation visit and continue to be collected at the same frequency as the treatment period during progression follow-up until BICR-

confirmed disease progression, then at disease progression and at week 8 (±3 days), week 16 (±3 days), and week 32 (±3 days) relative to the disease progression visit. PROs will not be collected for any patient after the primary PFS analysis.

o. The baseline assessments should be performed during the 28 day screening period and preferably as close as possible to and prior to the date of randomization. Subsequent assessments are to be performed every 8 weeks (±1 week) relative to randomization for the first 48 weeks and then every 12 weeks (±1 week) until objective radiological disease progression as per RECIST v1.1 as confirmed by BICR, even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment. Tumor assessment will be performed using contrast enhanced CT or MRI of the chest and abdomen (including liver and adrenal glands). Any other sites where disease is suspected or known at baseline must also be imaged. In addition contrast-enhanced MRI of the brain will be performed at all imaging timepoints. Duplicate images from all scans will be collected for independent review. Expedited analysis by BICR will be triggered upon investigator-assessed progression. Results of the BICR of scans for those patients with disease progression as assessed by the investigator will be reported back promptly to sites. Please refer to section 8.1.1 for more details. During Part II screening, radiotherapy planning scans from the definitive radiation treatment delivered prior to randomization are to be submitted to AstraZeneca's chosen imaging vendor.

p. If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit. Ensure genetic consent has be provided prior to sample collection. Blood samples for genetic analyses will not be collected in China as per local regulations.

q. Following BICR-confirmed progression, time to second progression on a subsequent treatment (PFS2) assessment will be performed by the investigator and defined according to local standard practice and may involve any of the following: objective radiological imaging (preferred), symptomatic progression, or death. Investigator assessment of subsequent response/progression to be collected every 12 weeks up to the data cut off for the primary PFS analysis.

r. Patient will be contacted for survival follow-up every 12 weeks. Patients should be contacted in the week after data cut-off for each study analysis (primary progression free survival [PFS] and OS) to establish survival status.

s. Study drug will only be dispensed to patient at randomization day (visit 2) after all study procedures and assessments have been performed as described in above table and all eligibility criteria are met.

t. Blood and tumor samples for exploratory biomarker analyses are not applicable for China as per local regulations.

u. Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and ethnicity during Part I screening or during Part II screening for patients who directly enter Part II. Smoking history will be collected at Part II for all patients.

v. Randomization will be made in IVRS/IWRS system as soon as all the eligibility criteria are met as confirmed by the investigator. Every effort should be made to minimize the time between randomization and starting study treatment. It is recommended that patients commence study treatment as soon as possible after randomization and whenever possible within one day. (i.e., on the same day after randomization in the IVRS/IWRS).

w. Patients who discontinue study treatment for a reason other than BICR-confirmed progression should have HRU module collected at that time of study treatment discontinuation and every 8 weeks up to week 48 and then every 12 weeks afterwards (relative to the date of randomization) until BICR-confirmed progression. Following BICR-confirmed progression, HRU module will be collected every 12 weeks during survival follow-up for all patients. Assessments for Healthcare resource will no longer be collected after the primary PFS analysis.

x. SAEs and AESIs (only if considered related to study treatment) will be collected throughout progression follow-up. SAEs and AESIs (only if considered related to open-label osimertinib) will be collected throughout survival follow-up.

y. Assessments for Healthcare resource will no longer be collected after the primary PFS analysis.

z. Treatment assignment may be unblinded for each patient who has BICR-confirmed PD. Patients receiving placebo may receive open-label osimertinib. Patients assigned to osimertinib may receive open-label osimertinib post progression if, in the opinion of their treating physician, they are continuing to derive clinical benefit (see Section 7.2).

aa. Only AEs and SAEs due to study procedures are to be collected during Screening Part I.

1.2 Synopsis

Principal investigators

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Protocol Title: A Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of osimertinib as maintenance therapy in patients with locally advanced, unresectable EGFR mutation-positive Non-Small Cell Lung Cancer (Stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy (LAURA)

Rationale:

Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers, and approximately 30% of patients present with Stage III disease. The standard treatment for patients with unresectable Stage III NSCLC is platinum-based doublet chemotherapy and radiotherapy (CRT) administered either concurrently (CCRT) for patients with a good performance status (PS) or sequentially (SCRT) for less fit patients, both with curative intent. A meta-analysis of concurrent versus (vs) sequential CRT in patients with epidermal growth factor receptor (EGFR) unselected Stage III NSCLC showed a small improvement in 5 year overall survival (OS) of 15.1% vs 10.6% for CCRT vs SCRT, respectively. In more recent trials with improved staging and delivery of chemoradiation, a 5 year OS rate of ~20%-30% has been observed in patients receiving CCRT.

There is limited data on outcomes for patients with EGFR mutation positive NSCLC receiving chemoradiation. The standard of care (SoC) for patients with unresectable EGFR mutation-positive NSCLC is the same as that for EGFR wildtype (EGFRwt) disease, i.e., chemoradiation. Whilst there is evidence that local control of disease following chemoradiation may be superior in EGFR mutation-positive patients, distant control is inferior and in particular, brain metastases occur more commonly (Ochiai et al 2016). As such, there is a strong rationale for use of maintenance therapy in this molecularly selected group of patients.

Osimertinib has demonstrated statistically significant superior progression-free survival (PFS) compared with an investigator choice of gefitinib or erlotinib in patients with first-line locally advanced or metastatic EGFR mutation positive NSCLC (median 18.9 months vs. 10.2 months; hazard ratio (HR) for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001). (FLAURA Soria et al 2017). Benefit was observed both in patients with and without brain metastases at baseline. At a later data cut-off, OS was statistically significantly longer for patients in the osimertinib arm compared with the SoC arm (median 38.6 months vs. 31.8 months; HR 0.7999;

95% CI 0.6409, 0.9963; p=0.0462) (Ramalingam et al 2020). These data in the first-line advanced setting provide support for evaluation of osimertinib in the even earlier disease setting of locally advanced unresectable NSCLC given the similar biology, i.e, EGFR-tyrosine kinase inhibitor (TKI) treatment-naïve NSCLC. The central nervous system (CNS) data observed with osimertinib in the FLAURA study is consistent with CNS efficacy data seen in patients with later lines of disease who have EGFR T790M positive NSCLC and indicate that osimertinib has the potential to delay or prevent the development of CNS metastases in patients with locally advanced unresectable NSCLC following chemoradiation.

Limited data from small prospective studies of EGFR TKI therapies in conjunction with chemoradiation or with radiation alone in patients with locally advanced unresectable EGFR mutation positive NSCLC and data from adjuvant trials of EGFR TKI therapies in EGFR mutation positive patients provide additional support for evaluation of osimertinib in this setting.

Thus administration of osimertinib following chemoradiation has the potential to prevent/delay disease progression, including in the CNS, prolong OS and potentially to increase the proportion of patients achieving 'cure' or long-term survival in comparison with chemoradiation alone.

Table 2 Study objectives

Primary objective:	**Endpoint/Variable:**
To assess the efficacy of osimertinib treatment compared with placebo as measured by progression free survival (PFS)	• PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1
Secondary objective:	**Endpoint/Variable:**
To assess the efficacy of osimertinib treatment compared with placebo by assessment of PFS in patients with: • EGFR Ex19del or L858R mutation • EGFRm+ Ex19del or L858R detectable in plasma-derived ctDNA	• PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1
To assess the efficacy of osimertinib versus placebo on CNS PFS	• Time to CNS PFS (time to the earliest of CNS progression or death) using BICR assessments according to RECIST v1.1 • Cumulative incidence rate of CNS PFS by BICR at 12 and 24 months
To further assess the efficacy of osimertinib compared with placebo	• OS • ORR • DoR • DCR and tumor shrinkage • TTDM All assessed by BICR according to RECIST v1.1 • TTD

Table 2 Study objectives	
To further assess the efficacy of osimertinib compared to placebo post progression	• PFS2 • TFST • TSST
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib compared with placebo	• Change from baseline in EORTC QLQ-C30 • Change from baseline in EORTC QLQ-LC13
To assess the safety and tolerability profile of osimertinib compared with placebo	• AEs (graded by CTCAE v5); • Clinical chemistry, hematology and urinalysis; • Vital signs (pulse and blood pressure), physical examination, weight; • ECG parameters; • LVEF; • WHO Performance Status.
To assess the PK of osimertinib	• Trough plasma concentrations of osimertinib, and its metabolite AZ5104 If conducted, PK Parameters ($CL_{ss/F}$, $C_{ss,\ min}$ and $C_{ss,\ max}$, AUC_{ss}) may be derived using population PK analysis and reported separately to the CSR. Data from this study may form part of a pooled analysis with data from other studies
Exploratory Objectives	**Endpoint/Variable:**
To assess potential treatment-related adverse effects in patients treated with osimertinib compared with placebo using PRO-CTCAE	The PRO-CTCAE questionnaire will be used to identify change in treatment-related symptoms
To assess the patients' overall impression of the severity of their cancer symptoms using PGIS	PGIS: Proportion of patients assessing current symptom severity
To compare osimertinib treatment with placebo treatment on health state utility	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data.
To compare health resource use associated with osimertinib treatment versus placebo	HRU Module
To investigate the relationship between osimertinib (and metabolite) PK and selected endpoints (which may include efficacy, safety and/or PRO), where deemed appropriate	Correlation of PK with other primary, secondary or exploratory endpoints in patients treated with osimertinib.*
To compare the baseline tumor EGFR mutation status in screened patients with evaluable results from baseline plasma samples Data may be used to support diagnostic development	Comparison of EGFR mutation status between tumor DNA) and plasma-derived ctDNA.
To compare the local EGFR mutation test result used for patient selection with the retrospective central **cobas®** EGFR Mutation Test v2 results from baseline tumor samples.	Comparison of EGFR mutation status between the local EGFR mutation test results and central **cobas®** EGFR Mutation Test v2 results from tumor samples with evaluable results.

Table 2 Study objectives

To collect and store DNA for future exploratory research into genes/genetic variation that may influence PK or response to osimertinib (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib or comparator.*
To assess the relationship between PK and blood-borne biomarkers.	Correlation of blood based biomarkers, including alterations in ctDNA, with variation in PK*.
To collect and store tumor samples to evaluate the association between exploratory biomarkers and key efficacy endpoints	Key markers to include, but not limited to mutations, amplifications, or expression changes in EGFR mutations, HER2 and MET.*
To collect and store plasma for isolation of ctDNA and to evaluate the association between exploratory biomarkers and key efficacy endpoints	Longitudinal analysis of ctDNA for mutations, amplifications or expression changes in EGFR, HER2, MET and other genes.*
To collect and store plasma to assess the relationship between blood borne biomarkers and key efficacy endpoints	Biomarkers will include but will not be limited to growth factors, or cytokines.*
To identify innate resistance mechanisms to study treatment.	Assessment of innate resistance mechanisms including but not limited to identify mutations, amplifications, or expression changes in EGFR, HER2 and MET in baseline ctDNA and/or tissue biopsies.*
To identify acquired resistance mechanisms to study treatment.	Assessment of resistance mechanisms including but not limited to identify mutations, amplifications, or expression changes in EGFR, HER2 and MET in ctDNA and/or tissue biopsies taken at time of disease progression.*
To conduct exploratory research on tissue and plasma samples into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to osimertinib (where response is defined broadly to include efficacy, tolerability or safety). Tissue and plasma samples may be used to support diagnostic development	Samples may be analyzed retrospectively for novel biomarker discovery research and/or diagnostic development.*

*Samples may be analysed retrospectively. The results of this research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this research may be pooled with data from other studies with the study drug to generate hypotheses to be tested in future research.

AE=adverse event; AUC_{ss}=area under plasma concentration-time curve during any dosing interval at steady state [amount·time/volume]; BICR=blinded independent central review; $CL_{ss/F}$=apparent total body clearance at steady state; CNS=central nervous system; CSR=clinical study report; $C_{ss,\,max}$=maximum plasma concentration at steady state; $C_{ss,\,min}$=minimum plasma concentration at steady state; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; DCR=disease control rate; DNA=deoxyribonucleic acid; DoR=duration of response; ECG=electrocardiogram; EGFR=epidermal growth factor receptor; EGFRm+ = EGFR mutation positive; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; EQ-5D-5L = EuroQoL 5-Dimension 5-Levels; Ex19del=Exon 9 deletion; HER2=human epidermal growth factor receptor 2; MET=tyrosine-protein kinase Met;; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS2=time to second progression on a subsequent treatment; PFS=progression-free survival; PGIS=Patients Global Impression of Severity; PK=pharmacokinetic(s); PRO=patient reported outcomes; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology

Table 2 Study objectives
Criteria for Adverse Events; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumors; TFST=Time to first subsequent therapy; TSST=Time to second subsequent therapy; TTD= Time to treatment discontinuation; TTDM=time to death or distant metastases; WHO=World Health Organization.

Overall design

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter international study assessing the efficacy and safety of osimertinib, as maintenance therapy in patients with locally advanced, unresectable EGFR mutation positive NSCLC (Stage III), whose disease has not progressed following definitive platinum-based chemoradiation therapy.

Study period

Estimated date of first patient enrolled is June 2018

Estimated date of last patient completed (OS cut off) is May 2025

Number of Patients

Approximately 200 patients will be randomized in a 2:1 ratio (osimertinib to placebo). Of those, it is planned that approximately 30 to 40 patients will be recruited in China.

Patients randomized will have achieved a complete response (CR), partial response (PR), or have stable disease (SD) following definitive, platinum-based, chemoradiation. Randomization will be stratified by: sequence of chemoradiation (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and will also include China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) as a stratification factor to allow separate randomization for the purposes of reporting in China.

In order to reflect global clinical practice, recruitment will be monitored on an ongoing basis and will be managed to ensure that the majority (≥60%) of patients entering the study have received prior CCRT. Study entry is permitted based on the detection of an Exon 19 deletion (Ex19del) and/or L858R mutation via central, tissue-based EGFR testing using the **cobas**® EGFR Mutation Test v2, or from a pre-existing local EGFR test result obtained using a tissue-based Food and Drug Administration (FDA)-approved Companion Diagnostic (CDx) for TAGRISSO (i.e., **cobas**® EGFR Mutation Test v2 or FoundationOne® CDx test) from a Clinical Laboratory Improvement Amendments (CLIA)-certified (United States of America [USA] sites) or an accredited local laboratory (sites outside of the USA).

Treatments and Treatment Duration

Patients will be randomized in a 2:1 ratio to one of two treatment arms as follows:

- Osimertinib 80mg oral (po) once daily (QD) until objective radiological disease

progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 which is confirmed by blinded independent central review (BICR) or until another treatment discontinuation criterion is met.

- Matching placebo 80 mg po QD until objective radiological disease progression per (RECIST) v1.1 which is confirmed by BICR or until another treatment discontinuation criterion is met.

Treatment assignment may be unblinded for each patient with BICR-confirmed progression per RECIST v1.1. Patients assigned to osimertinib may continue to receive osimertinib if, in the opinion of their treating physician, they are continuing to derive clinical benefit. Patients receiving placebo may receive open-label osimertinib, in accordance with local clinical practice and the judgement of their treating physician. Patients must not receive any other anti-cancer therapies between discontinuation of study treatment and the start of treatment with open-label osimertinib. For all patients, post-progression treatment with osimertinib may continue as long as the treating physician considers the patient to be deriving clinical benefit.

After the final OS analysis, AstraZeneca will continue to supply open-label osimertinib until the patient stops deriving clinical benefit (as judged by the investigator), or until osimertinib is commercially available for use in the first-line setting in the patients' respective country/territory.

Patients who discontinue study treatment for any reason prior to BICR-confirmed disease progression enter progression follow up and should continue to have tumor assessments according to the schedule of assessments until disease progression confirmed by BICR.

Patients who discontinue study treatment due to BICR-confirmed disease progression per RECIST v1.1 will enter survival follow up.

Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be convened, and will meet to review unblinded safety data, initially approximately 6 months after the study has started, as long as a minimum of 20 patients have been randomized and treated for >1 month. Three subsequent meetings will take place every 6 months and then meetings will be held yearly thereafter until primary analysis completion. 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.

Statistical methods

Approximately 200 patients will be randomized, globally, in a 2:1 ratio (osimertinib: placebo) to this study. These patients will be stratified by disease stage that chemoradiation

was received for (IIIA vs IIIB/IIIC), chemoradiation schedule (CCRT vs SCRT) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity). The primary endpoint of the study is PFS by BICR in the Full Analysis Set (FAS) population. The primary analysis of PFS will occur when approximately 120 progression events have been observed from the globally randomized patients. If the true PFS hazard ratio for the comparison of osimertinib vs placebo is 0.53, 120 progression events will provide 90% power to demonstrate a statistically significant difference in PFS at a 5% 2-sided significance level (translating to an approximate improvement in median PFS from 8 to 15 months assuming exponential data distribution and proportional hazards). The smallest treatment difference that would be statistically significant is a PFS HR of 0.68 (translating to an approximate 4m improvement).

The analysis of PFS in the China cohort will be conducted at the same time as the analysis of PFS for the overall population.

The final analysis of OS will be conducted at approximately 60% maturity when approximately 120 death events (across both arms) have occurred. Since two OS analyses are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the testing of two planned analyses of OS.

The final analysis of OS in the China cohort will be conducted at the same time as the final analysis of OS for the overall population.

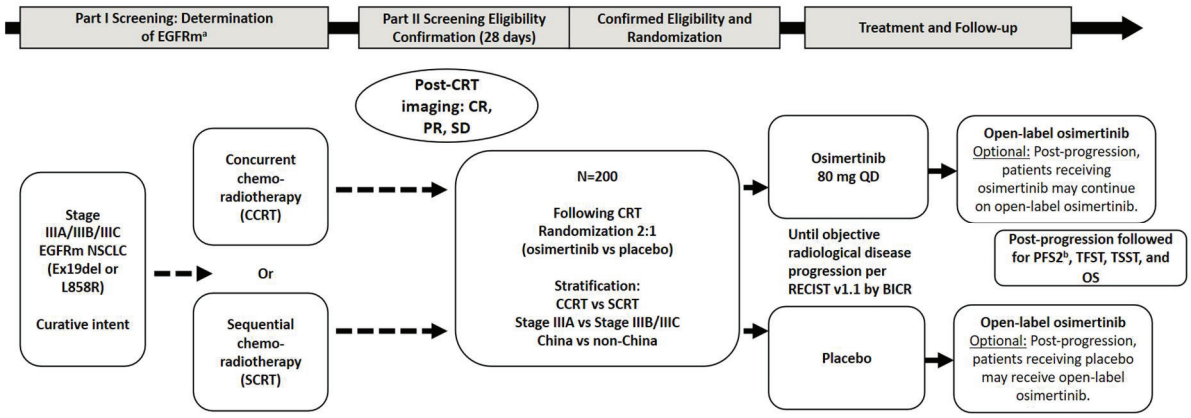
PFS will be analyzed using a log rank test stratified by chemoradiation schedule (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity). The primary analysis will be based on BICR assessment of disease progression by RECIST v1.1. A sensitivity analysis of PFS will be performed based on data assessed by investigator assessment for all patients.

The two secondary endpoints of OS and CNS PFS in the overall population will be tested sequentially after the primary PFS analysis in a hierarchical procedure at the time of the PFS analysis. OS will be tested sequentially after PFS in a hierarchical procedure at an interim (time of PFS analysis) and final (approximately 60% maturity) timepoint.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



Abbreviations: BICR=Blinded Independent Central Review; CR=complete response; CRT=chemoradiotherapy; EGFRm=EGFR mutation positive; Ex19Del=Exon 19 deletion; PFS2=time of second progression on a subsequent treatment; PR=partial response; OS=overall survival; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; SCRT=sequential chemoradiotherapy; TFST=time to first subsequent therapy; TSST=time to subsequent second therapy.

[a] Patients with a positive local EGFR test result via a tissue-based FDA approved CDx for TAGRISSO (i.e., **cobas**® EGFR Mutation Test v2 or FoundationOne® CDx test) do not need to undergo Part I screening.

[b] Assessment of PFS2 will not be collected after the primary PFS analysis

2 INTRODUCTION

2.1 Stage III Non-Small Cell Lung Cancer

Primary lung cancer is the most common form of cancer (12.9% of all new cancers worldwide) after non-melanocytic skin cancer and it remains the leading cause of cancer-related death overall (19.4% of all deaths from cancer) (GLOBOCAN 2012). NSCLC represents approximately 80% to 85% of all lung cancers.

Locally advanced NSCLC is defined as Stage III NSCLC according to the most recent (8th) Edition of the International Association for the Study of Lung Cancer (IASLC)/Union for International Cancer Control tumor/node/metastasis (TNM) staging classification (Goldstraw et al 2016). Stage III NSCLC represents a heterogeneous group of patients. At one end of the spectrum, patients with T3 and N1 disease are generally considered resectable. However, patients with T4 disease, i.e., that invades vital central structures (diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina) and/or patients with ipsilateral mediastinal nodal involvement (N2), ipsilateral distant nodal disease or contralateral nodal involvement (N3) are generally consider unresectable. The various combinations of T stage and nodal status determine whether disease is classified as Stage IIIA, IIIB or IIIC, which are associated with progressively poorer outcomes (Goldstraw et al 2016).

Given the heterogeneity in extent and distribution of disease in Stage III NSCLC, international guidelines recommend that an individualized decision on patient management must be made within a multidisciplinary team including pulmonologists, thoracic/medical oncologists, radiation oncologists, thoracic surgeons, radiologists and pathologists (National Comprehensive Cancer Network (NCCN) NSCLC 2018, Eberhardt et al 2015 [ESMO (European Society for Medical Oncology) Consensus Conference]) and treatment should be carried out in high-volume centers.

Based on a US National Cancer Database of 813,032 patients diagnosed with NSCLC between 1998 and 2006 and with available staging information, the proportion of patients diagnosed with Stage III disease was approximately 27% (Morgensztern et al 2010).

Whilst these patients have unresectable disease, they may still have disease that can be cured with definitive chemoradiation. CCRT is considered the SoC for younger patients with good performance status and minimal comorbidities. Based on a NSCLC Collaborative Group meta-analysis comparing CCRT with SCRT, CCRT was associated with a significant benefit on OS (HR, 0.84; 95% CI, 0.74 to 0.95; P =.004), with an absolute benefit of 4.5% at 5 years (15.1% vs 10.6%) (Aupérin et al 2010). However, CCRT was associated with increased Grade 3 to 4 acute esophageal toxicity (18% vs 4%). As such, SCRT is reserved for patients who are less fit.

In one study, only approximately 40% of patients were considered eligible for CCRT (De Ruysscher et al 2009). Advanced age, and cardiac and pulmonary comorbidities were the principal reasons for non-eligibility. Similarly, in a United Kingdom (UK) national survey

including 49 centers that evaluated the current practice of CCRT in patients with locally advanced unresectable disease, most of the respondents estimated that less than 30% of patients were suitable for CCRT (Helbrow et al 2012). Based on market research in the United States (US), Western Europe and Japan, of the patients that received chemoradiation treatment, the proportion varied from region to region however overall approximately two thirds of patients received CCRT and one third received SCRT (Kantar Health 2017).

Trials included in the NSCLC Collaborative Group meta-analysis were conducted in the late 1980's, 1990s and early 2000s, and did not include staging work-up consistent with current standards. In particular, most were not staged with positron emission tomography (PET) scans and brain magnetic resonance imaging (MRI) and it is known that approximately 10% to 30% of patients with non-metastatic NSCLC as determined by conventional imaging may be found to have distant metastases with more modern diagnostic tools (MacManus et al 2001, Pfister et al 2004). Moreover, most trials in the NSCLC Group meta-analysis used a two-dimensional radiotherapy technique and the total dose of radiotherapy was below modern day standards in two of the six trials. The median OS associated with CCRT in the larger trials in the meta-analysis was 16 to 17 months (Furuse et al 1999, Curran et al 2003, Curran et al 2011, Fournel et al 2005, Belderbos et al 2007).

As a consequence of improvements in (i) tumor staging (leading to stage migration); (ii) planning and delivery of radiotherapy, eg, intensity-modulated radiotherapy (IMRT); and (iii) management of toxicities associated with chemoradiation, efficacy outcomes associated with CCRT have improved. In more recent studies the median OS ranges from 20.6 to 28.7 months (Bradley et al 2015, Senan et al 2016, Liang et al 2017, Ahn et al 2015, Mitchell et al 2015) and in one study 5 year OS of 32% was observed (Bradley et al 2017)

In addition to the use of CCRT, studies of induction chemotherapy prior to CCRT or consolidation chemotherapy after CCRT have been conducted. A Phase III study of induction chemotherapy failed to show a survival benefit (Vokes et al 2007). Similarly three phase III randomized studies of consolidation therapy showed no OS benefit, (Hanna et al 2008, Ahn et al 2015; Flentje et al 2016) and this was confirmed in a meta-analysis that included five studies with a total of 958 patients (Odds Ratio [OR]=1.24; 95% CI: 0.89-1.72; P=0.21). They did find a significant increase in the risk of toxicity, including infection, pneumonitis and treatment-related death. (Chang et al 2016). In addition, a pooled analysis of 41 trials (34 Phase II Trials and 7 Phase III trials) including 45 arms (CCT+: 25; CCT−: 20) failed to provide evidence that consolidation chemotherapy after CRT yields significant survival benefit for locally advanced NSCLC (Tsujino et al 2013). In contrast, a meta-analysis of 5 studies with a total of 1036 patients found that consolidation chemotherapy after CCRT followed by consolidation chemotherapy improved OS (pooled HR 0.85; 95% CI 0.73-0.99; P = 0.03). (Wang et al 2017). Based on these data overall there is no consistent evidence that supports use of induction

chemotherapy or consolidation chemotherapy in conjunction with CCRT.

Studies in EGFR unselected patients indicate that patients with adenocarcinoma of the lung are less likely to progress at the primary site than patients with squamous cell carcinoma or large cell carcinoma following chemoradiation (Cox et al 1999). In contrast, patients with adenocarcinoma are more likely than patients with squamous cell carcinoma to develop metastases to the brain (Cox et al 1999, Hendriks et al 2016) and other distant sites (Cox et al 1999). The incidence of brain metastases as first site of relapse is 11-16% in patients with adenocarcinoma or non-squamous carcinoma (Cox et al 1999, Senan et al 2016), compared with 8% in patients with squamous cell carcinoma (Cox et al 1999). In one study approximately 27% of patients with Stage III adenocarcinoma developed symptomatic brain metastases following chemoradiation compared with approximately 7% of patients with stage III squamous cell cancer (Hendriks et al 2016). However, these differences in recurrence patterns have not led to different management strategies for these different entities.

Recently durvalumab, a selective, high-affinity, human IgG1 monoclonal antibody that blocks programmed death ligand 1 (PD-L1) binding to programmed death 1 (PD-1) and CD80, was approved for use in patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. Approval was based on data from a Phase III randomized placebo-controlled study in which durvalumab was associated with a significant prolongation of PFS compared with placebo given as a maintenance therapy in patients without disease progression after two or more cycles of definitive concurrent platinum-based chemoradiation (median PFS from randomization 16.8 months (95% CI, 13.0 to 18.1) with durvalumab vs 5.6 months (95% CI, 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; P<0.001) (Antonia et al 2017). As a result of these data National Comprehensive Cancer Network (NCCN) guidelines 2018 recommend durvalumab as a consolidation (maintenance) therapy in patients whose disease has not progressed following definitive CCRT (National Comprehensive Cancer Network (NCCN) NSCLC 2018).

In this study, EGFR mutations were observed in 6.0% of the patients (6.1% in the durvalumab group, and 5.9% in the placebo group. The observed treatment effect was in favor of durvalumab in the EGFR positive patients (PFS HR: 0.76; 95% CI: 0.35, 1.64). However, these results should be interpreted with caution due to the small number of patients who were EGFR positive (29 in the durvalumab group and 14 in the placebo group) and the small number of events (17 in the durvalumab group and 11 in the placebo group).

There are no other approved maintenance therapies following chemoradiation in patients with stage III NSCLC.

2.2 Locally advanced unresectable EGFR mutation positive NSCLC

2.2.1 Incidence and management

The proportion of patients with adenocarcinoma that is EGFR mutation-positive appears broadly similar across stages and is approximately 50% to 60% in Asian patients and 15% to 20% in patients from the West (Shi et al 2014, Wu et al 2014, Dogan et al 2012). However, in predominantly single center retrospective studies that assessed the relative outcome of efficacy of chemoradiation in patients with EGFR wildtype (EGFRwt) and EGFR mutation-positive tumors, the incidence of EGFR mutation-positivity in patients with adenocarcinoma appeared lower than expected in Asian patients (20% to 30%) (Tanaka et al 2015, Yagishita et al 2015, Akamatsu et al 2014, Hayashi et al 2012) but was as expected in Western patients (Mak et al 2011, Komaki et al 2015).

The SoC for patients with locally advanced unresectable EGFR mutation positive NSCLC is the same as that for EGFRwt NSCLC i.e., chemoradiation of curative intent.

International guidelines indicate that there is currently no role for EGFR-TKIs in the management of locally advanced EGFR mutation-positive NSCLC, a consequence of which is that EGFR mutation testing is not universally considered to be standard practice. (Eberhardt et al 2015 [ESMO Consensus Conference], Saijo et al 2010 [Lung Cancer Working Group Report], Tan et al 2016 [IASLC Consensus Statement]. However, enrolment into randomized trials to address the potential for benefit in this population is encouraged (Tan et al 2016 [IALSC Consensus Statement]. As such, Study D5160C00048 has been designed to assess the potential benefit of osimertinib in this patient group.

2.2.2 Efficacy outcomes following chemoradiation in patients with locally advanced unresectable EGFR mutation-positive NSCLC

The literature on outcomes of chemoradiation in patients with locally advanced EGFR mutation positive NSCLC is limited and is largely based on single center retrospective analyses, together with some small prospective studies.

2.2.2.1 Prospective Studies

Whilst there are numerous published Phase III studies of chemoradiation in patients with unresectable EGFR-unselected NSCLC (Ahn et al 2015, Bradley et al 2015, Mitchell et al 2015, Senan et al 2016, Liang et al 2017, Curran et al 2011,Bradley et al 2017, Butts et al 2014), there are no Phase III studies that have assessed the efficacy outcomes of chemoradiation in patients with EGFR mutation-positive disease.

Xing and colleagues reported preliminary data at American Society of Clinical Oncology (ASCO) 2017 from a multicenter, randomized, open-label, Phase II trial that compared etoposide/cisplatin with concurrent radiotherapy vs erlotinib with concurrent radiotherapy followed by maintenance erlotinib for up to 2 years. The primary endpoint was PFS. Forty-one patients were enrolled into the erlotinib (n=20) and etoposide/cisplatin (n=21) arms. Compared with etoposide/cisplatin, the median PFS in the erlotinib arm was significantly improved (27.86 vs 6.41 months;HR: 0.053, 95% CI: 0.006 to 0.463; P<0.001) (Xing et al

2017). OS data from this study are not available at this time.

In a very small, prospective, randomized, Phase II trial in patients with Stage III EGFR mutation-positive NSCLC, induction erlotinib, chemoradiation concurrent with erlotinib followed by 6 cycles of consolidation erlotinib (Arm A; n=7) was compared with induction erlotinib and subsequent chemoradiation (Arm B; n=5). Median PFS and OS were numerically longer in Arm A than Arm B. In Arm A and Arm B, median PFS was 11.6 months (95% CI 0.1 to 23.2) vs 8.1 months (95% CI 2.7 to 13.6) , respectively, and median OS was 39.3 months (95% CI, 0.7 to 83.3) vs 31.2 months (95% CI, 0.1 to 90.2) (p=0.442), respectively (Lee et al 2017)

Another small prospective single arm study (n=8) assessed afatinib induction, followed by chemoradiation and surgery if feasible, then adjuvant afatinib for up to two years (Warren et al 2016). At a median follow-up of 24 months, 7/8 of patients were recurrence-free.

2.2.2.2 Retrospective Studies

Data on the relative efficacy of chemoradiation in patients with unresectable EGFR mutation-positive NSCLC compared with EGFRwt NSCLC are available from a number of retrospective studies, predominantly from single institutions (Tanaka et al 2015, Yagishita et al 2015, Li et al 2011, Lim et al 2017, Ahn et al 2013, Mak et al 2011, Komaki et al 2015, Hayashi et al 2012, Akamatsu et al 2014, Ishihara et al 2017) or multi-institutions (Ready et al 2010).

Across the studies, patient numbers are generally small and there is marked heterogeneity with respect to disease characteristics at baseline, prior chemoradiation regimen employed and whether additional treatment strategies are permitted, eg, surgery (Mak et al 2011, Ahn et al 2013, Warren et al 2016) or EGFR-TKIs (Ready et al 2010, Lee et al 2017, Komaki et al 2015, Warren et al 2016). As such, these data should be interpreted with caution.

Across studies of chemoradiation without surgery or EGFR-TKIs, the median PFS ranges from 6.3 to 13.1 months in patients with EGFR mutation-positive NSCLC (Xing et al 2017,Tanaka et al 2015, Yagishita et al 2015, Akamatsu et al 2014, Hayashi et al 2012, Ishihara et al 2017 and 9.5 to 18.6 months in patients with EGFRwt NSCLC (Tanaka et al 2015, Yagishita et al 2015, Akamatsu et al 2014, Hayashi et al 2012, Ishihara et al 2017). In two of these studies, the PFS was statistically significantly lower in the EGFR mutation-positive group (Tanaka et al 2015; Ishihara et al 2017); no significant differences were observed in the remaining studies. Overall based on these data the median PFS in the EGFR mutation-positive groups was either similar or lower than that observed in the EGFRwt groups.

A more detailed analysis of data indicates that EGFR mutation status impacts upon the patterns of disease recurrence after chemoradiation for locally advanced NSCLC and highlights that patients with EGFR mutation-positive tumors are more likely to have superior local control but inferior distant control, including brain metastases, compared with patients with EGFRwt tumors (predominantly adenocarcinoma). Specifically Ochiai

and colleagues performed a literature review and pooled analysis of data from three studies, including 76 patients with EGFR mutation-positive tumors and 270 patients with EGFRwt tumors (Ochiai et al 2016; Tanaka et al 2015, Yagishita et al 2015, Akamatsu et al 2014).

Patients with EGFR mutation-positive tumors were more likely to be female (OR 4.94, P<0.001) and never-smokers (OR 11.10, P<0.001) and were less likely to have advanced T-stage (OR 0.14, P<0.001) compared with patients with EGFRwt tumors. No significant difference was observed between the EGFR mutation-positive group and EGFRwt group for objective response rate (ORR; OR 1.46, 95% CI, 0.79-2.70, P=0.228) or disease recurrence (OR 1.37, 95% CI, 0.68 to 2.75, P=0.379). However compared with patients with EGFRwt tumors, there was a lower incidence of local/locoregional progression (OR 0.35, 95% CI, 0.18 to 0.71, P=0.003) and a higher incidence of distant progression (OR 2.97, 95% CI, 1.59 to 5.54, P<0.001) in patients with EGFR mutation-positive tumors. Moreover, brain metastasis was the most frequent site of disease relapse in the EGFR mutation-positive group in two studies (Tanaka et al 2015, Akamatsu et al 2014) and across the studies the incidence was significantly higher in the EGFR mutation-positive group, 26.3% vs 11.1%, (OR 2.75, 95% CI, 1.43 to 5.31, P=0.003) (Ochiai et al 2016).

Additional studies of chemoradiation (+/- additional treatment strategies) have revealed similar findings with a statistically significant higher risk of distant progression (Ahn et al 2013, Ishihara et al 2017) or statistically significant lower risk of local progression (Lim et al 2017, Mak et al 2011) in the EGFR mutation-positive group compared with the EGFRwt group.

Additional studies of chemoradiation (+/- additional treatment strategies) have revealed a statistically significant lower incidence of advanced T-stage (Lim et al 2017) or a trend towards lower incidence of advanced T-stage in patients with EGFR mutation-positive tumors compared to EGFRwt (Ahn et al 2013; Mak et al 2011).

Across studies of chemoradiation without surgery or EGFR-TKI, the median OS ranges from 37.1 to 67.5 months in patients with EGFR mutation-positive NSCLC and 21.1 to 42.9 months in patients with EGFRwt NSCLC (Tanaka et al 2015, Yagishita et al 2015, Akamatsu et al 2014, Hayashi et al 2012, Tanaka et al 2015). Median OS was higher in the EGFR mutation-positive groups compared with EGFRwt groups, but there were no statistically significant differences between the groups in these studies.

In other studies that have allowed additional treatment strategies, the median OS in the EGFR mutation-positive groups has been either significantly longer (Lee et al 2017), numerically longer (Mak et al 2011; Komaki et al 2015) or numerically lower than in the EGFRwt groups (Ready et al 2010)

In three studies, post-progression survival was statistically significantly longer in patients with EGFR mutation-positive NSCLC compared with EGFRwt NSCLC (Yagishita et al 2015, Lee et al 2017, Ishihara et al 2017).

2.2.2.3 Summary of data on demography/disease characteristics and efficacy outcomes for patients with locally advanced EGFR mutation positive NSCLC

Patients with EGFR mutation-positive tumors are more likely to be female, never-smokers and are less likely to have advanced T-stage tumors compared with patients with EGFRwt tumors. There are limited data on the outcomes of CCRT in patients with unresectable EGFR mutation-positive cancer. In comparison with patients with unresectable EGFRwt NSCLC (predominantly adenocarcinoma), for patients with EGFR mutation-positive NSCLC:

(i) The median PFS is similar or lower.

(ii) Within this, locoregional control is superior and distant control inferior – the brain is a common site of relapse.

(iii) Median OS is generally longer, likely due in part to administration of EGFR-TKIs at the time of disease progression.

2.3 Study rationale

Whilst definitive chemoradiation is given as a treatment of curative intent for patients with Stage III disease, the majority of patients will subsequently have disease progression and hence these patients have a high unmet medical need. The increased risk of distant metastases including brain metastases, observed in patients with EGFR mutation NSCLC following chemoradiation supports the rationale for administration of an effective systemic therapy with an oral EGFR TKI therapy. Of the available EGFR TKI therapies clinical data indicate that osimertinib has the greatest potential to provide benefit in this setting.

In addition to demonstrating efficacy in patients with T790M positive disease treated in the ≥second-line setting (Mok et al 2017a, Goss et al 2016, Yang et al 2016, Yang et al 2017) osimertinib has demonstrated benefit in patients with previously untreated, locally advanced or metastatic EGFR mutation-positive NSCLC (FLAURA- Soria et al 2017). In a randomized Phase III study comparing osimertinib with a standard EGFR-TKI (gefitinib or erlotinib) with a primary endpoint of PFS, PFS was significantly longer with osimertinib than with standard EGFR-TKIs (median 18.9 months vs. 10.2 months; HR for disease progression or death, 0.46; 95% CI, 0.37 to 0.57; P<0.001). Data on OS were immature at the PFS analysis (25% maturity). At a later data cut-off (OS maturity 57.7%), OS was statistically significantly longer for patients in the osimertinib arm compared with the SoC arm (median 38.6 months vs. 31.8 months; HR 0.7999; 95% CI 0.6409, 0.9963; p=0.0462) (Ramalingam et al 2020).

The PFS benefit for osimertinib compared with standard EGFR-TKIs (gefitinib or erlotinib) was observed both in patients with (n=116) and without CNS metastases at study entry (n=440) (HR 0.47 [95% CI 0.30, 0. 74 p=0.0009] and 0.46 [95% CI 0.36, 0.59]; p<0001 for patients with and without CNS metastases respectively) (Ramalingam et al 2017).

In an analysis of patients with at least 1 CNS lesion (measurable or non-measurable) at baseline as determined by CNS BICR, (23% of all randomized patients), there was a nominally statistically significant and clinically meaningful improvement in CNS PFS for patients on osimertinib compared to patients on SoC (HR=0.48, 95% CI 0.26, 0.86; P=0.014) (Reungetwattana et al 2018). As the CNS PFS analysis was third in the hierarchical statistical testing strategy, this improvement was formally statistically significant following the statistically significant improvement in OS (Ramalingam et al 2020). Irrespective of CNS metastasis status at study entry, based on Investigator assessment, there were fewer patients with new CNS lesions in the osimertinib arm compared to the SoC arm (11/279 [3.9%] vs. 34/277 [12.3%], respectively) [Data on File]. In the subgroup of patients with a CNS metastasis status of "No" at baseline, there was a lower number of patients with newly identified CNS lesions as reason for progression in the osimertinib arm compared to the SoC arm (7/226 [3.1%] vs. 15/214 [7.0%], respectively) [Data on File.]

Further evidence of the activity of osimertinib in the CNS has been demonstrated in patients with T790M positive disease. In the pooled Phase II studies of 128 patients with CNS metastases on baseline brain scans, 50 patients had lesions that were evaluable for response. Confirmed CNS ORR and disease control rate (DCR) were 54% (27/50; 95% CI 39, 68), and 92% (46/50; 95% CI 81, 98), respectively (Goss et al 2017). In addition in AURA3 osimertinib showed a significantly longer CNS PFS (cFAS; 11.7 vs 5.6 months; HR 0.32; 95% CI 0.15, 0.69; p = 0.004) and higher CNS ORR (cEFR; 70% vs 31%; (OR, 5.13; 95% CI 1.44, 20.64; p = 0.015)) compared with chemotherapy in patients with CNS metastases at baseline (Mok et al 2017b).

EGFR TKIs have demonstrated efficacy in reducing the risk of disease recurrence in patients with EGFRm NSCLC in adjuvant trials which represents an analogous setting to the D5160C00048 study i.e., maintenance treatment following therapy of curative intent in patients with non-metastatic EGFR mutation positive NSCLC. Further details are provided in Section 4.2.4.

The data outlined in Section 2.2.2 demonstrating the propensity for patients with EGFR mutation positive tumors to relapse with distant metastases, including brain metastases, provide a strong rationale for administration of an effective systemic therapy in this population of patients. Positive efficacy data with osimertinib in comparison with EGFR TKI SoC in patients with first line advanced NSCLC in the FLAURA trial provide strong support for the evaluation of osimertinib in the even earlier disease setting of locally advanced unresectable NSCLC given the similar biology, i.e., in patients with EGFR-TKI treatment-naïve NSCLC. Moreover limited data from small prospective studies of EGFR TKI therapies in conjunction with chemoradiation or with radiation alone in patients with locally advanced unresectable EGFR mutation positive NSCLC and from adjuvant trials in patients with EGFR m+ NSCLC provide additional support for evaluation of osimertinib in this setting.

Thus administration of osimertinib following chemoradiation has the potential to

prevent/delay disease progression, including in the CNS, and potentially to increase the proportion of patients achieving 'cure' or long-term survival in comparison with chemoradiation alone.

2.4 Background

Osimertinib (TAGRISSO™) is an oral, potent, selective, CNS active, irreversible EGFR-TKI, effective against both EGFR-TKI-sensitizing mutations (EGFR mutation) as well as T790M mutation positive ([T790M mutation positive] TKI resistance conferring mutation) forms of EGFR.

As of 12 November 2017, osimertinib is marketed in 63 countries worldwide 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.

As of 12 November 2017, it is estimated that (i)10820 patients and 118 healthy volunteers have been enrolled into the clinical development and early access programs and real world treatment study, of which 10,414 subjects have received osimertinib and (ii) the post-marketing exposure is estimated to be ~13,500 patient-years cumulatively.

Osimertinib was evaluated in a Phase I (AURA1) trial over a range of 20 mg QD to 160 mg QD. No dose limiting toxicities were observed and objective responses were seen at all doses. On the basis of the totality of the safety, pharmacokinetic and preliminary efficacy data, 80 mg QD was selected as the recommended Phase II dose (Janne et al 2015).

Two Phase II studies (AURA ex and AURA 2 were conducted in patients with T790M positive disease (second line or greater) following prior use of an EGFR TKI therapy. In the pooled 411 pre-treated EGFR T790M mutation positive patients, the ORR BICR in the evaluable for response population was 66% (95% CI: 61, 71) (Yang et al 2016). ORRs by BICR above 50% were observed in all pre-defined subgroups analyzed, including line of therapy, race, age and region. In patients with a confirmed response by BICR, the median duration of response (DoR) was 12.5 months (95% CI: 11.1, not evaluable). The median PFS by BICR was 11.0 months 95% CI (9.6, 12.4). Median OS was 26.8 months (24.2, not calculable) (Mitsudomi et al 2017).

Osimertinib was evaluated in a Phase III, open-label, randomized study (2:1 ratio [osimertinib: platinum-based doublet chemotherapy]) to assess the efficacy and safety of osimertinib (80 mg, PO, QD) vs platinum-based doublet chemotherapy (pemetrexed plus carboplatin or pemetrexed plus cisplatin followed by optional pemetrexed maintenance) as second-line therapy in patients with advanced EGFR T790M mutation positive NSCLC who had progressed following treatment with 1 line of treatment with an approved EGFR-TKI. The primary endpoint was PFS as assessed by the investigator.

In total, 419 patients were randomized: 279 in the osimertinib arm and 140 in the chemotherapy arm. There was a statistically significant and clinically meaningful

improvement in PFS for patients on osimertinib vs. patients on chemotherapy based on investigator assessment (HR: 0.30 [95% CI: 0.23, 0.41]; p-value: <0.001). The median PFS was 10.1 months (95% CI: 8.3, 12.3) in the osimertinib arm vs. 4.4 months (95% CI: 4.2, 5.6) in the chemotherapy arm (Mok et al 2017a). In addition osimertinib was associated with statistically significant improvements in secondary endpoints of ORR, DoR, DCR and tumor shrinkage compared with chemotherapy.

In addition osimertinib was evaluated in previously untreated, EGFR mutation-positive NSCLC in the FLAURA study as described in Section 2.3.

In clinical trials osimertinib has been generally well –tolerated. Based on a review of 1142 patients with EGFR mutation positive NSCLC who received osimertinib at a dose of 80 mg daily in two randomized Phase III studies (FLAURA, first-line; AURA3, second-line only), two single arm Phase II studies (AURA ex; AURA2, second-line or greater) and one Phase I study (AURA1, first-line or greater) most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhea (49%) and rash (47%). Grade 3 and Grade 4 adverse reactions with osimertinib were 9.7% and 0.9%, respectively.

In patients treated with osimertinib 80 mg QD, dose reductions due to adverse reactions occurred in 2.1 % of the patients. Discontinuation due to adverse reactions was 4.3%.

Osimertinib has not been associated with gastrointestinal perforations or hemorrhagic diarrhea and no events leading to dehydration or renal failure have been reported. No severe bullous, blistering or exfoliative skin conditions were observed.

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.9% and were fatal in 0.4% (n=5) of the 1142 patients who received osimertinib in the FLAURA and AURA studies. The incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of non- Japanese Asian ethnicity and 2.8% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months. In the FLAURA study comparing osimertinib with a SoC EGFR TKI (gefitinib or erlotinib) in patients with previously untreated locally advanced or metastatic EGFR mutation positive NSCLC, ILD was reported in a low but numerically higher proportion of patients in the osimertinib arm than in the SoC arm (osimertinib: 3.9%; SoC: 2.2%). Serious adverse events (SAEs) were reported in 2.2% of patients in the osimertinib arm and 1.4% of patients in the SoC arm; and were Common Terminology Criteria for Adverse Events (CTCAE) grade 3 in 3 (1.1%) patients on osimertinib and 2 (0.7%) patients on SoC; no patients had CTCAE Grade 4 events in the osimertinib arm vs 2 patients (0.7%) in the SoC arm. No grade 5 events were observed in either treatment group.

Of the 1142 patients in FLAURA and AURA studies treated with osimertinib 80 mg, 0.9% of patients were found to have a corrected QT (QTc) greater than 500 msec, and 3.6% of patients had an increase from baseline QTc greater than 60 msec. No QTc-related

arrhythmia events were reported in the FLAURA or AURA studies.

A pharmacokinetic (PK) analysis with osimertinib predicted a concentration-dependent increase in QTc interval prolongation. (14.2 msec with an upper bound (90% CI) of 15.8 msec).

Keratitis was reported in 0.7% of the 1142 patients treated with osimertinib in the FLAURA and AURA studies.

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 3.9% (35/908) of patients treated with osimertinib who had baseline and at least one 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.

Additional information including pre-clinical and clinical data on osimertinib may be found in the Investigator's Brochure.

2.5 Benefit/risk assessment

2.5.1 Potential benefits

Section 2.3 provides the data that support the rationale that for evaluation of osimertinib in study D5160C00048, in particular data demonstrating superior PFS and CNS PFS for osimertinib in comparison with EGFR TKI SoC in patients with previously untreated, EGFR mutation-positive NSCLC (FLAURA [Soria et al 2017]). Administration of osimertinib following chemoradiation has the potential to prevent/delay disease progression, including in the CNS, and potentially to increase the proportion of patients achieving 'cure' or long-term survival in comparison with chemoradiation alone.

2.5.2 Overall risks

This is the first study to evaluate the use of osimertinib in patients with unresectable Stage III NSCLC within 6 weeks of completion of chemoradiation in patients whose disease has not progressed and as such the safety of administering osimertinib in this setting is unknown.

Section 2.4 provides information on the safety profile of osimertinib based on the program of AstraZeneca Phase I-III studies of patients with EGFR TKI -Naïve first line EGFR mutation-positive disease and patients with ≥second line T790M mutation positive NSCLC. Osimertinib has been generally well–tolerated in these trials.

Safety topics potentially of relevance to the use of osimertinib given post-chemoradiation include ILD/Radiation pneumonitis and changes in cardiac contractility.

2.5.3 ILD/Radiation pneumonitis

In addition to the risk of drug-induced ILD, radiation treatment is also associated with pneumonitis. In recently published trials of patients with locally advanced unresectable

EGFR unselected NSCLC the incidence of ≥Grade 3 pneumonitis ranged from approximately 1% to 8.3% (Flentje et al 2016, Ahn et al 2015, Senan et al 2016, Bradley et al 2015, Liang et al 2017, Antonia et al 2017). With the exception of one trial where the rate of fatal pneumonitis was 4.2% to 5.2% (Liang et al 2017), the incidence of fatal pneumonitis in these trials was <2%.

The Phase III study comparing the anti–programmed death ligand 1 (PD-L1) antibody durvalumab with placebo as consolidation therapy (maintenance therapy) in patients with Stage III NSCLC whose disease had not progressed after CCRT, has a similar design to this study of osimertinib (Antonia et al 2017). In this study the incidence of all grade pneumonitis or radiation pneumonitis in the placebo arm was 24.8%, with Grade 3 or 4 events occurring in 3.0 % of patients. Grade 5 adverse events (AEs) of pneumonitis and radiation pneumonitis occurred in 1.3% and 0.4% respectively of patients in the placebo arm.

First or second generation EGFR TKIs, gefitinib and erlotinib have been given solely as maintenance treatment in patients following chemoradiation in two placebo-controlled studies (Kelly et al 2008, Rigas et al 2009) and two single arm studies (Casal Rubio et al 2014, Warren et al 2016). In a study comparing gefitinib and placebo following chemoradiation and maintenance docetaxel in patients with EGFR unselected NSCLC the incidence of Grade 3/4 pneumonitis in patients receiving gefitinib was 2.8% compared with no patients on placebo. (Kelly et al 2008). No fatal events were observed. No excess of ≥ Grade 3 pneumonitis was reported in studies by Rigas et al 2009, Casal Rubio et al 2014 and Warren et al 2016.

Other trials have assessed the use of first generation EGFR TKIs given concurrently with radiotherapy or CRT followed by maintenance EGFR TKI. These include two small randomized trials (Martinez et al 2016, Xing et al 2017) and eight single arm studies (Center et al 2010, Ready et al 2010, Wang et al 2011, Stinchcombe et al 2008, Niho et al 2012, Socinski et al 2012, Zhuang et al 2014, Okamoto et al 2011). No consistent excess of ≥Grade 3 radiation pneumonitis or ILD compared with control groups or historical controls was observed.

There is a theoretical risk however that the incidence and/or severity of pneumonitis observed in D5160C00048 (LAURA) in patients receiving osimertinib could be higher than has been observed in trials of osimertinib in patients who have not recently undergone radiation treatment or in trials of chemoradiation (in the absence of osimertinib).

Enrollment criteria and guidelines for management of toxicities will be included in the protocol to reduce the risk of severe pneumonitis (drug-induced and/or radiation induced).

Whilst recognizing that radiographic changes coinciding with radiation portals would favor the diagnosis of radiation pneumonitis, differentiating a potential drug-induced pneumonitis from radiation pneumonitis can be challenging. As such a single guidance on dosing modification and toxicity management for ‘pneumonitis’ is provided in

Section 8.4.4.2 which covers the medical concepts of pneumonitis/ILD and radiation pneumonitis.

Whilst patients with ≥Grade 3 pneumonitis require permanent discontinuation from study treatment, the guidance permits re-challenge with study treatment in patients who develop Grade 2 pneumonitis following resolution of symptoms. This recommendation is supported by a review of the AstraZeneca global safety database as of September 2017 which identified 46 patients with osimertinib-related ILD who either continued osimertinib (n=11) or temporarily stopped and subsequently received re-challenge with osimertinib (n=35) (Data on File). Most were considered SAEs (37/46). The majority of cases were from a Japanese post-marketing surveillance study D5160C00025 (n=31/46). Some cases have been reported in the literature (Mamesaya et al 2017a Mamesaya et al 2017b, Miyauchi et al 2017, Nagasaka and Gadgeel 2017).

Of the 35 cases where osimertinib was temporarily stopped the majority were treated with steroids (29/35). In 16/35 case reports osimertinib was reintroduced alongside steroid treatment. Osimertinib was reintroduced at a dose of 80 mg QD in 17/35 case reports; in 12/35 case reports the dosage was reduced from 80 mg QD to 40 mg QD. In the remaining cases where information was known, patients received 80mg every other day (EOD) or continuation of 40 mg QD. Recurrence of ILD was reported in 5 patients (14%), none of which were fatal. Of these 3/17=18% had ILD recurrence at a dose of 80 mg QD and 2/14 =14% had ILD recurrence following a dose reduction to <80 mg QD. In 21 cases no recurrence of ILD was reported and in 9 patients information was not available.

Of the 11 case reports of ILD where osimertinib was continued six were treated with steroids.1/11 treatment was continued at the same dosage, in 1 case report the dosage was changed to 80 mg EOD, and in 2 case reports the dosage was changed to 40 mg EOD. A total of 8/11 reported an outcome of recovered or recovering, and 3/11 were ongoing at the time of the report.

2.5.3.1 Effects on Cardiac Contractility

Whilst based on the available clinical trial data, AstraZeneca considers that a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established, for patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Radiotherapy –associated heart toxicity has long been recognized in patients with breast cancer or Hodgkin lymphoma, with increases in cardiovascular events and deaths typically noted 10 or more years after treatment (Wang et al 2017). Recent data indicates that for patients with unresectable Stage III NSCLC receiving chemoradiation, heart dose is a predictor of the risk of radiation-associated cardiac toxicity (Wang et al 2017) and of OS (Speirs et al 2017). It has been suggested that radiotherapy-associated cardiac toxicity after treatment of Stage III NSCLC may occur earlier than historically understood (Wang et al

2017). As such it is recommended that heart dose is minimized.

The D5160C00048 protocol provides recommendations for maximum radiation exposure of the heart. In addition, consistent with other trials of osimertinib, cardiac function will be monitored with baseline assessment of LVEF and every 12 weeks thereafter via echocardiogram (ECHO)/ multigated acquisition scan (MUGA) scans. Additional scans will also be performed as clinically indicated.

2.5.3.2 Maintenance Studies of EGFR TKI therapies in patients with EGFR unselected Stage III NSCLC

In a study of gefitinib vs placebo as maintenance treatment following CCRT and docetaxel consolidation in patients with EGFR unselected inoperable Stage III NSCLC, a statistically significant deficit in survival was observed for gefitinib (SWOG S0023-Kelly et al 2008). The reasons for this observation are unclear. Data on EGFR mutation status in the study is unavailable, however given that this study was conducted in the US it is likely that only a minority of patients would have had EGFR mutation positive tumors. Moreover erlotinib was not associated with a deficit in survival compared with placebo as maintenance treatment following CCRT in patients with EGFR unselected Stage III NSCLC in a trial conducted in the US (Rigas et al 2009). Given that Study D5160C00048 will be conducted exclusively in patients with EGFR mutation positive NSCLC, the adverse effect of gefitinib on survival in the SWOG0023 is not considered to be of clinical concern.

2.5.4 Overall benefit/risk

Although there can be no certainty of clinical benefit to patients, the positive efficacy data for osimertinib from the Phase III trial in patients with first line advanced NSCLC, supported by studies of EGFR TKI therapies in the adjuvant setting and the Phase II study of erlotinib in conjunction with chemoradiation (RECEL) provide support for evaluation of osimertinib in patients with locally advanced unresectable EGFRm NSCLC.

Osimertinib is generally well tolerated. The majority of adverse reactions are of Grade 1 or 2 severity, and the most frequent reactions are typical EGFR-TKI side effects including rash and diarrhea. ILD or ILD-like ADRs (e.g. pneumonitis) are commonly reported (3.9% of patients in Phase I-III studies), and occasionally fatal (0.4%) for patients receiving osimertinib. Enrolment criteria, safety monitoring and toxicity management guidance, including specific guidance for pneumonitis, have been included in the protocol to prevent and manage severe toxicity.

It is therefore, reasonable and appropriate to evaluate the oral administration of maintenance treatment with osimertinib in comparison to placebo both following chemoradiation in patients with locally advanced unresectable EGFR mutation positive NSCLC (Stage III) according to the proposed study.

3 OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/Variable:**
To assess the efficacy of osimertinib treatment compared with placebo as measured by progression free survival (PFS)	• PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1
Secondary objective:	**Endpoint/Variable:**
To assess the efficacy of osimertinib treatment compared with placebo by assessment of PFS in patients with: • EGFR Ex19del or L858R mutation • EGFR Ex19del or L858R mutation detectable in plasma-derived ctDNA	• PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1
To assess the efficacy of osimertinib versus placebo on CNS PFS	• Time to CNS PFS (time to the earliest of CNS progression or death) using BICR assessments according to RECIST v1.1 • Cumulative incidence rate of CNS PFS by BICR at 12 and 24 months
To further assess the efficacy of osimertinib compared with placebo	• OS • ORR • DoR • DCR and tumor shrinkage • TTDM All assessed by BICR according to RECIST v1.1 • TTD
To further assess the efficacy of osimertinib compared to placebo post progression	• PFS2 • TFST • TSST
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib compared with placebo	• Change from baseline in EORTC QLQ-C30 • Change from baseline in EORTC QLQ-LC13
To assess the safety and tolerability profile of osimertinib compared with placebo	• AEs (graded by CTCAE v5) • Clinical chemistry, hematology, and urinalysis • Vital signs (pulse and blood pressure), physical examination, weight • ECG parameters • LVEF • WHO Performance Status
To assess the PK of osimertinib	• Trough plasma concentrations of osimertinib, and its metabolite AZ5104 If conducted, PK Parameters ($CL_{ss/F}$, $C_{ss,\,min}$ and $C_{ss,\,max}$, AUC_{ss}) may be derived using population PK analysis and reported separately to the CSR. Data from this study may form part of a pooled analysis with data from other studies

Table 3 Study objectives

Exploratory Objectives	Endpoint/Variable:
To assess potential treatment-related adverse effects in patients treated with osimertinib compared with placebo using PRO-CTCAE	The PRO-CTCAE questionnaire will be used to identify change in treatment-related symptoms
To assess the patients' overall impression of the severity of their cancer symptoms using PGIS	PGIS: Proportion of patients assessing current symptom severity
To compare osimertinib treatment with placebo treatment on health state utility	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data.
To compare health resource use associated with osimertinib treatment versus placebo	HRU Module
To investigate the relationship between osimertinib (and metabolite) PK and selected endpoints (which may include efficacy, safety and/or PRO), where deemed appropriate	Correlation of PK with other primary, secondary or exploratory endpoints in patients treated with osimertinib.*
To compare the baseline tumor EGFR mutation status in screened patients with evaluable results from baseline plasma samples Data may be used to support diagnostic development	Comparison of EGFR mutation status between tumor DNA and plasma-derived ctDNA.
To compare the local EGFR mutation test result used for patient selection with the retrospective central **cobas®** EGFR Mutation Test v2 results from baseline tumor samples.	Comparison of EGFR mutation status between the local EGFR mutation test results and central **cobas®** EGFR Mutation Test v2 results from tumor samples with evaluable results.
To collect and store DNA for future exploratory research into genes/genetic variation that may influence PK or response to osimertinib (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib or comparator.*
To assess the relationship between PK and blood-borne biomarkers.	Correlation of blood based biomarkers, including alterations in ctDNA, with variation in PK*.
To collect and store tumor samples to evaluate the association between exploratory biomarkers and key efficacy endpoints	Key markers to include, but not limited to mutations, amplifications, or expression changes in EGFR mutations, HER2 and MET.*
To collect and store plasma for isolation of ctDNA and to evaluate the association between exploratory biomarkers and key efficacy endpoints	Longitudinal analysis of ctDNA for mutations, amplifications or expression changes in EGFR, HER2, MET and other genes.*
To collect and store plasma to assess the relationship between blood borne biomarkers and key efficacy endpoints	Biomarkers will include but will not be limited to growth factors, or cytokines.*
To identify innate resistance mechanisms to study treatment.	Assessment of innate resistance mechanisms including but not limited to identify mutations, amplifications, or expression changes in EGFR, HER2 and MET in baseline ctDNA and/or tissue biopsies.*

Table 3 Study objectives	
To identify acquired resistance mechanisms to study treatment.	Assessment of resistance mechanisms including but not limited to identify mutations, amplifications, or expression changes in EGFR, HER2 and MET in ctDNA and/or tissue biopsies taken at time of disease progression.*
To conduct exploratory research on tissue and plasma samples into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to osimertinib (where response is defined broadly to include efficacy, tolerability or safety). Tissue and plasma samples may be used to support diagnostic development	Samples may be analyzed retrospectively for novel biomarker discovery research and/or diagnostic development.*

*Samples may be analysed retrospectively. The results of this research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this research may be pooled with data from other studies with the study drug to generate hypotheses to be tested in future research.

AE=adverse event; AUC_{ss}=area under plasma concentration-time curve during any dosing interval at steady state [amount·time/volume]; BICR=blinded independent central review; $CL_{ss/F}$=apparent total body clearance at steady state; CNS=central nervous system; CSR=clinical study report; $C_{ss, max}$=maximum plasma concentration at steady state; $C_{ss, min}$=minimum plasma concentration at steady state; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; DCR=disease control rate; DNA=deoxyribonucleic acid; DoR=duration of response; ECG=electrocardiogram; EGFR=epidermal growth factor receptor; EGFRm+ = EGFR mutation positive, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; EQ-5D-5L = EuroQoL 5-Dimension 5-Levels; Ex19del=Exon 19 deletion; HER2=human epidermal growth factor receptor 2; MET=tyrosine-protein kinase Met; MUGA=multigated acquisition; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS2=time to second progression on a subsequent treatment; PFS=progression-free survival; PGIS=Patients Global Impression of Severity; PK=pharmacokinetic(s); PRO=patient reported outcomes; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumors; TFST=Time to first subsequent therapy; TSST=Time to second subsequent therapy; TTD= Time to treatment discontinuation; TTDM=time to death or distant metastases; WHO=World Health Organization.

4 STUDY DESIGN

4.1 Overall design

This is a Phase III double-blind, randomized, placebo-controlled, multicenter international study assessing the efficacy and safety of osimertinib as a maintenance therapy in patients with locally advanced unresectable (Stage III), NSCLC centrally confirmed EGFR mutations (Ex19del and L858R) whose disease has not progressed following definitive platinum based-chemoradiation therapy.

Accounting for patients who do not have EGFR Ex19del or L858R mutation detected, sample attrition and 85% screen fail rate for other reasons, in order to randomize approximately 200 patients, it is estimated that 1333 patients will be screened at approximately 130 sites in Asia, Europe, North America and South America. It is assumed that approximately 80% of patients will be recruited from Asia and approximately 20% from non-Asian countries.

Approximately 200 patients will be randomized. Of those, it is planned that approximately

30 to 40 patients will be recruited in China. This is being done to ensure adequate Chinese patient participation to satisfy China Regulatory Authority requirements. The China cohort will support standalone safety and efficacy analyses of patients from China.

Study entry is permitted based on the detection of an Ex19del and/or L858R mutation via central, tissue-based EGFR testing using the **cobas®** EGFR Mutation Test v2, or from a pre-existing local EGFR test result obtained using a tissue-based FDA-approved CDx for TAGRISSO (i.e., **cobas**® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA).

Patients without a pre-existing local EGFR test result will be required to undergo a two-stage screening process. In Part I screening, patients will be asked to consent to provide a recent tumor tissue sample for central prospective EGFR mutation testing using the **cobas**® EGFR Mutation Test v2. Consent can be given for prospective testing of the tumor sample before, during, or after chemoradiation. Part II screening will be conducted following completion of chemoradiation and will be carried out in patients who have passed Part I screening i.e. have tumors that contain the Ex19del or L858R mutations. In addition, patients with an EGFR mutation-positive test result (Ex19del and/or L858R) based on a local EGFR test using a tissue-based FDA-approved CDx for TAGRISSO (i.e., **cobas**® EGFR Mutation Test v2 or FoundationOne® CDx test), can enter Part II screening directly after completion of chemoradiation. For these patients investigators will be asked to provide a formalin-fixed and paraffin embedded (FFPE) tumor tissue sample, where available, for retrospective central analysis of EGFR mutation status in Part II screening for comparison with the local test. However, patient enrolment will be based upon the local test.

Following completion of chemoradiation, all patients will be required to have a baseline CT scan (preferred) or MRI scan (chest and abdomen including liver and adrenal glands) and contrast-enhanced MRI of the brain ≤28 days prior to randomization. Patients whose disease has not progressed are eligible for the study. Patients must have sufficiently recovered from chemoradiation prior to randomization with no unresolved toxicity of CTCAE>Grade 2. Patients who meet all of the inclusion criteria and none of the exclusion criteria for this study will be randomized 2:1 to receive either osimertinib or placebo. Randomization must occur ≤ 6 weeks following completion of chemoradiation. Patients will be stratified by prior chemoradiation strategy (CCRT vs SCRT), tumor stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs. enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) to allow separate randomization for China.

In order to reflect global clinical practice, recruitment will be monitored on an ongoing basis and will be managed to ensure that the majority (approximately ≥60%) of patients entering the study have received prior CCRT.

Following randomization, treatment should continue until objective radiological disease

progression occurs as defined by RECIST v1.1 and as confirmed by BICR or until another discontinuation criterion is met.

Tumor assessments will be performed using (i) CT scan (preferred) or MRI, each preferably with contrast, of the chest and abdomen (including liver and adrenal glands) and additional anatomy imaging, as indicated by signs and symptoms of the patient; and (ii) contrast-enhanced T1w MRI of the brain.

CT /MRI of chest/abdomen and MRI of the brain will be performed at all tumor imaging visits. The baseline assessment is part of the screening procedure. Objective tumor assessments will be made every 8 weeks (relative to the date of randomization) until 48 weeks, then every 12 weeks thereafter, until objective radiological disease progression occurs as defined by RECIST v1.1 and as confirmed by BICR. Additional scans should be performed if clinically indicated, i.e., if disease progression is suspected. If an unscheduled assessment is performed, and the patient's disease has not progressed per BICR, every attempt should be made to perform the subsequent assessments at their scheduled visits. Patients who discontinue trial therapy for any reason prior to BICR-confirmed disease progression should continue to have tumor assessments according to the schedule of activities (SoA; irrespective of the reason for stopping study drug and/or subsequent therapy). All imaging assessments (including unscheduled visit scans) will be sent to the AstraZeneca appointed central reader on an ongoing basis. Expedited Analysis by BICR will be triggered upon investigator-assessed progression. Results of the BICR of scans for patients with investigator-assessed disease progression will be reported back promptly to sites. Since the primary analysis of the study is based on BICR, it is important that study treatment and scheduled imaging assessments continue until progression by BICR is confirmed. If a subject has been deemed to have objective disease progression according to the investigator tumor assessment by RECIST v1.1, but it is not confirmed by BICR, study treatment should be continued and the patient should maintain tumor assessments according to the SoA. Investigators should notify the Clinical Research Organization (CRO) again when progression is assessed at a subsequent timepoint. Progression includes disease recurrence for subjects with no evidence of disease at baseline.

Patients will undergo safety assessments at baseline, Week 2, Week 4 and every 4 weeks until Visit 9/Week 24, every 8 weeks until Visit 12/Week 48, then every 12 weeks afterwards until treatment discontinuation.

Safety assessments will include clinical chemistry, hematology, urinalysis, electrocardiogram (ECG) and LVEF measurement with ECHO/MUGA scans. Tumor and blood sampling for biomarker analysis will be performed. PK sampling will also be performed. Patient reported outcomes (PROs) and health resource use (HRU) for monitoring patient's health condition and HRU respectively will be collected during the course of the study. Following discontinuation of study drug, a treatment discontinuation visit will be performed. AEs/SAEs/AEs of special interest (AESIs) will be collected for 28 days following discontinuation and followed-up until resolution. Thereafter, at any time, if an investigator learns of any SAEs (including death) or AESI possibly related to study

treatment or open-label osimertinib, AstraZeneca should be notified. See Section 8.3 for further information on AE reporting.

Treatment assignment may be unblinded for each patient with BICR-confirmed progression per RECIST v1.1. Patients assigned to osimertinib may continue to receive open-label osimertinib if, in the opinion of their treating physician, they are continuing to derive clinical benefit. Patients assigned to placebo may receive open-label osimertinib, in accordance with local clinical practice and the judgement of their treating physician. Patients must not receive any other anti-cancer therapies between the discontinuation of study treatment and the start of treatment with open-label osimertinib. Treatment with open-label osimertinib should continue until radiological or clinical progression or unacceptable toxicity as determined by the investigator, at which point open-label osimertinib will be discontinued.

Patients with BICR-confirmed progression per RECIST v1.1 will enter **survival follow-up**. See Section 7.1.1.2 for details of data collection requirements during survival follow-up both prior to and post the primary PFS analysis. Any SAEs and any AESIs considered related to study treatment or open-label osimertinib should be reported during survival follow-up (See Section 8.3.2).

If a patient has discontinued study treatment for a reason other than BICR confirmed objective radiological disease progression per RECIST v1.1, the patient will enter **progression follow-up** and will continue to have regular scheduled tumor assessments until BICR-confirmed progression per RECIST v1.1, together with additional assessments as defined in Section 7.1.1.1. Any SAEs considered related to study treatment or study procedures should be reported during progression follow-up (See Section 8.3.2).

Patients will be followed as per the study protocol until data cut-off for the primary analysis when approximately 120 BICR-confirmed PFS events have occurred. This is estimated to occur approximately 48 months following first patient randomized, based on a 40 month recruitment period. Results from the primary analysis will be reported in the Clinical Study Report (CSR). The study blind will be broken (at the Sponsor level) at the time of the primary PFS analysis. Sites and subjects will remain blinded until study completion i.e., after final OS analysis.

Following the primary PFS analysis patients who are continuing to receive study treatment will have study assessments as per the schedule of assessments.

Following the primary PFS analysis patients who are continuing to receive study treatment will have their tumor assessment in accordance with local clinical practice. Formal RECIST measurements will not be collected. Study treatment should continue until disease progression as determined by the investigator, or until a treatment discontinuation criterion is met, at which point study treatment will be discontinued. BICR confirmation of progression is not required (see Section 7.5).

For all patients receiving open-label osimertinib, treatment with open-label osimertinib should continue until radiological or clinical progression or unacceptable toxicity as determined by the investigator, at which point open-label osimertinib will be discontinued.

The final analysis of OS will be conducted at approximately 60% maturity when approximately 120 death events (across both arms) have occurred. After the final OS analysis, the study blind will be broken and AstraZeneca will continue to supply open-label osimertinib until the patient stops deriving clinical benefit (as judged by the investigator), or until osimertinib is commercially available for use in the first-line setting in the patients' respective country/territory.

4.2 Scientific rationale for study design

4.2.1 Rationale for 2:1 randomization schedule

The use of a 2:1 randomization has been selected to increase the chance that patients randomized into this study will receive osimertinib treatment, given the potential benefit of osimertinib in this setting.

4.2.2 Rationale for choice of comparator

As described in Section 2, based on the results of a placebo-controlled Phase III trial, the PD-L1 inhibitor durvalumab is approved for use (in the US) in patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy and is recommended in the 2018 NCCN guidelines as a consolidation (maintenance therapy) for use in this patient population (Antonia et al 2017). In this study the HR for PFS in the EGFR mutant subgroup was 0.76, in favor of durvalumab, with a wide CI that crossed 1.0. The numbers of patients with EGFR mutation-positive tumors was small with few events; thus interpretation of the data from this subgroup should be made with caution. As such it is considered acceptable to compare osimertinib with placebo in the current study.

4.2.3 Rationale for selection of chemoradiation regimens

As described in Section 2, the SoC for patients with locally advanced unresectable Stage III NSCLC is CCRT, which has been shown to be superior to SCRT. However the magnitude of benefit is considered small (De Ruysscher et al 2016) and CCRT is associated with more toxicity. As a consequence of this only 30-40% of patients are eligible to receive CCRT.

Given that the unmet medical need is high regardless of whether CCRT or SCRT is given and considering that the degree of benefit for osimertinib compared with placebo is anticipated to be large and is likely to be similar, enrolment of both populations is permitted. Prior use of CCRT vs SCRT will however be included as a stratification factor.

The 2015 ESMO treatment guideline on the treatment of locally advanced (Stage III) NSCLC defines CCRT as simultaneous (same-day) administration of an active chemotherapy in parallel to ongoing thoracic radiotherapy fractions. SCRT is defined as

giving upfront combination chemotherapy for several cycles followed by a block of fractionated radiotherapy only (for 5–7 weeks). In the meta-analysis comparing 'concomitant vs sequential radiochemotherapy' concomitant chemotherapy was defined as chemotherapy administered during radiotherapy and sequential chemotherapy was defined as chemotherapy given before and/or after radiotherapy (Aupérin et al 2010). Two to three cycles of platinum-based chemotherapy were administered in the SCRT regimens (where chemotherapy was only given prior to radiation) in the studies that contributed to this meta-analysis (Furuse et al 1999, Curran et al 2003, Ulutin et al 2000, Fournel et al 2005, Belderbos et al 2007) with 2 cycles of platinum-based chemotherapy administered in the two largest studies (RTOG9410[Curran et al 2003] and WJLCG [Furuse et al 1999]).

Recognizing the considerable variation in clinical practice with respect to choice of chemotherapy, radiation dose and timing of chemotherapy in relation to delivery of radiation, inclusion criteria (Section 5.1) provide specific details of regimens that constitute CCRT and SCRT. Randomization will be carried out ≤6 weeks following completion of chemoradiation and the final chemotherapy cycle must end prior to, or concurrently with, the final dose of radiation (See Section 5.1 for clarification). Given the absence of consistent evidence to support the use of consolidation chemotherapy following CCRT (see Section 2) and the intent to introduce trial therapy as early as possible to maximize the potential for clinical benefit, consolidation chemotherapy is not permitted in the study.

4.2.4 Rationale for proposed treatment duration

Whilst in trials of chemoradiation in patients with EGFR unselected Stage III NSCLC the majority of progression events may be expected to have occurred by approximately three years, there is insufficient published data specifically in patients with EGFR mutation positive Stage III NSCLC to determine the optimal duration of treatment in the trial.

Data from adjuvant trials of EGFR TKI therapies in patients with EGFR mutation positive disease support dosing to progression in this study. Specifically in a randomized open label Phase III study (ADJUVANT/CTONG1104-NCT01405079) 222 patients with completely resected, Stage II–IIIA (N1–N2), EGFR mutant NSCLC were randomly assigned to either four cycles of adjuvant vinorelbine plus cisplatin or 24 months of gefitinib in a 1:1 ratio (Zhong et al 2018). Approximately two-thirds of the patients had Stage IIIA disease. Disease-free survival (the primary endpoint) was significantly longer for patients assigned gefitinib than for those assigned cisplatin-based chemotherapy (median 28·7 months, 95% CI 24·9–32.5 *vs* 18.0 months, 13.6–22.3; HR 0.60, 95% CI 0.42– 0.87; p=0.0054). However, after 24 months, the Kaplan-Meier (KM) curves for disease-free survival began to converge, meeting by 36 months, with no apparent tail of non-recurrent patients in either treatment group by 48 months. At the time of the analysis, OS data are not yet mature; 34% of events had occurred at data cut-off; 41 patients assigned to gefitinib and 35 assigned to vinorelbine plus cisplatin had died.

Similar KM curves for disease-free survival were reported for the subgroup of 161 patients

with EGFR-mutant disease identified retrospectively in the RADIANT trial, in which patients with Stage IB–IIIA disease were randomly assigned to erlotinib or placebo for 24 months after adjuvant chemotherapy (Kelly et al 2015). Disease-free survival was longer with erlotinib than with placebo (median 46·4 months *vs* 28·5 months; HR 0.61, 95% CI 0.38–0.98;), however this result was not statistically significant because of hierarchical testing. The disease-free survival curves began to converge from around 36 months, meeting by about 48 months. The OS data are immature with 35 deaths (22%) reported in the EGFR mutation subgroup (HR,1.09; 95% CI,0.545 to 2.161; *P*=.815).

In addition, in a single arm trial of 100 patients with Stage IA–IIIA EGFR-mutant disease receiving 2 years of erlotinib after adjuvant chemotherapy, disease-free survival at 24 months was 89%, however the survival curve declined thereafter, towards a tail of 60% non-recurrent (presumably cured) disease at 4 years (Pennell et al 2014)

Collectively these data suggest that EGFR TKIs may prolong disease free survival through effective suppression of tumor growth during treatment but may not eliminate microscopic disease and hence may not be curative (Zhong et al 2018; Ng and Camidge 2018).

Whilst these data are from a different population to the proposed study population, both populations represent maintenance treatment following therapy of curative intent in patients with non-metastatic EGFR mutation positive NSCLC. As such these data are considered to be of relevance in determining the recommended duration of trial therapy. Treatment will continue until RECIST v1.1 defined disease progression and confirmed by BICR, or until another discontinuation criterion is met.

There have been no new specific adverse reactions or more severe known adverse reactions that have been observed with long term osimertinib therapy that would preclude dosing until progression in this study.

4.2.5 Rationale for primary endpoint of PFS

The primary endpoint of this study is PFS. PFS represents a direct effect of osimertinib's efficacy as it is not confounded by the efficacy of subsequent therapies used after disease relapse. It is accepted as a surrogate endpoint for clinical benefit in studies of patients with both advanced cancer (PFS and OS) and in patients with earlier stages of cancer (adjuvant disease-free survival).

Moreover, based on a re-analysis of meta-analyses of individual patients' data from 29 trials involving 5211 patients, PFS has been shown to be a valid surrogate for OS in assessment of chemotherapy and radiotherapy in patients with locally advanced disease (Mauguen et al 2013).

Given the long post-progression survival anticipated in this setting and the confounding effects of subsequent lines of therapy that may include osimertinib, it would be difficult to detect an OS benefit in this setting. Nevertheless, OS is one of the study's secondary endpoints and will serve to complement the PFS results.

A PFS HR of 0.53 will be targeted which translates to an improvement of 7 months on an estimated median PFS of 8 months (see Section 9.2) which constitutes a clinically meaningful benefit in this patient population. Assessment of disease status after chemoradiation is known to be complex, as the majority of patients will be expected to have treatment-related radiographic changes (Bledsoe et al 2017). As such, in order to ensure the most robust assessment of the primary endpoint, PFS will be assessed by BICR. The study will also include assessment of post–progression outcomes, including time to second progression on a subsequent treatment (PFS2) and time to subsequent treatments, in order to allow a robust characterization of the efficacy of osimertinib.

4.2.6 Rationale for the secondary efficacy endpoint of time to CNS progression

As described in Section 2.2.2.2 brain metastases occur more frequently in patients with locally advanced EGFR mutation-positive NSCLC following chemoradiation compared with EGFRwt disease following chemoradiation (OR 2.75, 95% CI, 1.43 to 5.31, P=0.003) (Ochiai et al 2016).

Brain metastases are associated with poor median survival, ranging from 3 to 8 months (Mak et al 2015, Berger et al 2013). Whole brain radiotherapy (WBRT) is the standard treatment for patients with brain metastases in particular for multiple intracranial lesions. Whole brain radiotherapy results in improvement, or in most cases stabilization, in neurological symptoms, but is frequently associated with significant comorbidities and radiation-related side effects, including delayed, progressive and irreversible cognitive dysfunction in long-term survivors (Lin and DeAngelis 2015). In patients who received WBRT alone, median survival rates of 2.4 to 4.8 months have been reported (Fan et al 2014). In addition, the recent QUARTZ study suggests that WBRT offers no substantial benefit to most patients with brain metastases secondary to NSCLC in terms of improved survival, overall quality of life (QoL) or reduction in steroid use (Mulvenna et al 2016).

Surgical resection for single brain lesions and stereotactic radiosurgery for oligometastatic disease is also used to manage brain metastases. However, good performance status and control of the extra-cranial disease is required in order to implement these techniques, and patients with CNS metastasis secondary to NSCLC are often not considered suitable candidates for surgery or radiosurgery (Fan et al 2014, Zimmermann et al 2014).

As demonstrated in Section 2.3 osimertinib has demonstrated compelling activity in the CNS in patients with EGFR TKI NSCLC and in patients with ≥second-line T790M positive NSCLC.

Given the poor prognosis of patients who develop brain metastases, in this study osimertinib has the potential to improve PFS and OS by delaying or preventing the development of CNS metastases. In addition, it may provide clinically meaningful benefit by avoiding consequences of neurological deficits from brain metastasis or by delaying/preventing long-term side effects associated with steroid use and brain irradiation. Time to CNS PFS will be assessed using BICR assessments according to RECIST v1.1. MRI with intravenous (IV) gadolinium diethylenetriamine penta-acetic acid

(Gd-DTPA) contrast enhancement currently is the procedure of choice, because MRI is more sensitive and specific than other imaging modalities in determining the presence, location, and number of metastases (Kruger et al 2011,Schellinger et al 1999,Yokoi et al 1999).

As such all patients will have Gd-DTPA contrast-enhanced T1w MRI brain scans at baseline and at the time of each RECIST tumor assessment to provide the most accurate assessment of time to CNS PFS.

4.3 Justification for dose

Osimertinib 80 mg or matching placebo will be administered PO, QD. This dose was initially selected for evaluation in clinical trials on the basis of the totality of the safety, PK and preliminary efficacy data in a Phase I study (Janne et al 2015).

Osimertinib 80 mg QD is the approved dose for use in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy and is the dose that has been evaluated in additional Phase III trials in the first line setting (FLAURA) and in the adjuvant setting (ADAURA). The safety profile of this dose is considered acceptable for use in the setting of maintenance post chemoradiation.

4.4 End of study definition

For the purpose of Clinical Trial Transparency (CTT) 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 defines two completion dates:

    - Primary Completion Date – the date that the final patient 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 – the date the final patient 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 patient'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 if they have completed all phases of the study including the last scheduled visit or last scheduled assessment, as shown in the SoA (Table 1), including OS determination.

The end of the study is defined as the last expected visit/contact of the last patient undergoing the study.

The study is expected to start patient enrolment June 2018 and to end by approximately May 2025.

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. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with osimertinib.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

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 assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.5.

In this protocol, "enrolled" patients are defined as those who sign the informed consent form (ICF) in this study at screening. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

As per standard, patient number (E-code) is assigned to the patient via an interactive voice response system/interactive web response system (IVRS/IWRS) once consent for screening is obtained and Investigator or delegate should perform screening call in IVRS/IWRS.

For procedures for withdrawal of incorrectly enrolled patients see Section 5.6.

5.1 Inclusion Criteria

5.1.1 Part I Screening

Part I screening applies only to patients that do not have a pre-existing local EGFR test result, derived from a tissue-based FDA-approved CDx for TAGRISSO (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use.

Patients are eligible to be included in Part I of the study only if all of the following inclusion criteria, and none of Part II screening exclusion criteria numbers 1, 2, 7, 9-11 and 15-20 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 informed consent for Part I screening form prior to any mandatory provision of tumor samples for testing of EGFR mutation status.

The ICF process is described in Appendix A 3.

Age and Sex

3. Male and Female patient must be aged at least 18 years. Patients from Japan aged at least 20 years.

Type of patient and disease characteristics

4. Patients with histologically documented NSCLC of predominantly non-squamous pathology* who present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology).

   **Patients with a stage III tumor of squamous histology who have a pre-existing local positive test result (Ex19del or L858R), irrespective of EGFR test used or lab accreditation, are eligible for Part I screening.*

   It is recommended but not required that except for overt cT4 disease, nodal status N2 or N3 should have been proven by biopsy, via endobronchial ultrasound, mediastinoscopy, or thoracoscopy or in absence of biopsy, should have been confirmed with whole body ^{18}F-fluoro-deoxyglucose PET plus contrast-enhanced CT in addition to or in combination with PET.

5. Patient who can provide an unstained formalin-fixed paraffin embedded tumor tissue* sample in a quantity sufficient to allow for prospective central analysis of EGFR mutation status.

   ** An archived tissue or new biopsy specimen, when no archived tissue is available, is acceptable. Patients should only have a new biopsy if it is considered a medically acceptable risk by the investigator.*

Further information is provided in Section 8.1.1 and in the laboratory manual.

5.1.2 Part II Screening

Part II screening applies to: (i) patients that have a pre-existing local EGFR mutation-positive (Ex19del or L858R) test result, derived from a tissue-based FDA-approved CDx for TAGRISSO (i.e., **cobas®** EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use; or (ii) patients who completed Part I screening and have centrally-confirmed EGFR mutation (Ex19del or L858R) positive NSCLC.

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 for the main study prior to any mandatory study specific procedures, sampling, and analyses.

3. Provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis for inclusion in the optional genetic research.

Note: If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study for optional test, 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.

Age and Sex

4. Male and Female patient must be aged at least 18 years. Patients from Japan aged at least 20 years.

Type of patient and disease characteristics

5. Patients with histologically documented NSCLC of predominantly non-squamous pathology* who present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology).

   **Patients with a Stage III tumor of squamous histology who have a pre-existing local positive test result (Ex19del or L858R), irrespective of EGFR test used or lab accreditation, and confirmed by central testing during Part I screening, are eligible for Part II screening.*

   It is recommended but not required that except for overt cT4 disease, nodal status N2 or N3 should have been proven by biopsy, via endobronchial ultrasound, mediastinoscopy, or thoracoscopy or in absence of biopsy, should have been confirmed with whole body ^{18}F-fluoro-deoxyglucose PET plus contrast-enhanced CT in addition to or in combination with PET.

6. The tumor harbors one of the two common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, as assessed by a tissue-based FDA-approved CDx for TAGRISSO (i.e., **cobas**® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA); or by central testing (using the **cobas**® EGFR Mutation Test v2).

7. Patients must not have had disease progression during or following definitive platinum-based, chemoradiation therapy.

8. Patients must have received either CCRT or SCRT regimens as defined below:

   - CCRT: Patients must have received at least 2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum–based chemotherapy) concurrent with radiation therapy, which must be completed ≤6 weeks prior to randomization. The final chemotherapy administration must be completed prior to, or concurrently with, the final dose of radiation. Note: A final cycle of chemotherapy is permitted up to 7 days after the last dose of radiation, if at least 2 cycles have already been given concurrently. Consolidation chemotherapy after radiation is not permitted but administration of chemotherapy prior to CCRT is permitted.

   - SCRT: SCRT is defined as chemotherapy followed by radiation therapy and not radiation therapy followed by chemotherapy. Patients must have received at least 2 cycles of platinum-based chemotherapy prior to radiation treatment, which must be completed ≤6 weeks prior to randomization. Consolidation chemotherapy after radiation is not permitted

   - If a patient has received at least 2 cycles of platinum-based chemotherapy and subsequently receives one cycle of platinum-based chemotherapy or < 5 doses of weekly platinum–based chemotherapy concurrent with radiation therapy, this will be considered SCRT

   - If a patient has received 1 cycle of platinum-based chemotherapy and subsequently receives one cycle of platinum-based chemotherapy or < 5 doses of weekly platinum–based chemotherapy concurrent with radiation therapy, this will not be considered CCRT or SCRT and the patient will not be eligible

9. The platinum-based chemotherapy regimen must contain one of the following agents: etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed, according to the local SoC regimens. Gemcitabine is permitted if used prior to radiation but not with radiation.

   Where possible, chemotherapy regimens should be given according to NCCN or ESMO guidelines.

10. Patients must have received a total dose of radiation of 60 Gy ±10% (54 to 66 Gy) as part of the chemoradiation therapy in order to be randomized. It is recommended but not required that patients eligible for randomization have a:

    - Mean lung dose <20 Gy and/or V20 <35%

    - Mean esophagus dose <34 Gy

    - Heart V50 <25%, V30 ≤50%, and V45 <35%

11. World Health Organization (WHO) performance status of 0 or 1 at Part II screening and Day 1.

12. Life expectancy >12 weeks at Day 1.

Reproduction

13. 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 adequate contraceptive measures, must not be breast feeding, and must have a negative pregnancy test prior to first dose of study drug; or female patients must have an evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

    - Female patients less than 50 years old would be consider postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with 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

14. Male patients must be willing to use barrier contraception, i.e., condoms (see Section 5.3).

5.2 Exclusion Criteria

5.2.1 Part I Screening

Patients are eligible to be included in Part I of the study only if none of the following Part II Screening exclusion criteria: 1, 2, 7, 9-11, and 15-20.

5.2.2 Part II Screening

Patients are eligible to be included in Part II screening process only if none of the exclusion criteria apply:

Medical conditions

1. Mixed small cell and NSCLC histology

2. History of ILD prior to chemoradiation

3. Symptomatic pneumonitis following chemoradiation.

4. Any unresolved toxicity CTCAE > Grade 2 from the prior chemoradiation therapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by

study drug may be included (e.g. hearing loss) after consultation with the AstraZeneca medical monitor.

5. Any of the following cardiac criteria:

   - Mean resting QTc >470 msec, obtained from 3 ECGs
   - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block.
   - Patient with 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 (CLQTS), family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes (TdP).

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

6. Inadequate bone marrow reserve or organ function, as demonstrated by any of the following laboratory values:

   - Absolute neutrophil count <1.5 x 10^9/L
   - Platelet count <100 x 10^9/L
   - Hemoglobin <90 g/L
   - Alanine aminotransferase (ALT) >2.5x the upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) >2.5x ULN
   - Total bilirubin (TBL) >1.5x ULN or >3x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia)
   - Creatinine >1.5x ULN concurrent with creatinine clearance <30 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5xULN

7. History of other malignancies, except: adequately treated non-melanoma skin cancer or lentigo maligna, curatively treated in-situ cancer, or other solid tumors curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinion of the treating physician, do not have a substantial risk of recurrence of the prior malignancy.

8. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol. Active infection including hepatitis B virus (HBV), hepatitis C and human immunodeficiency virus (HIV). Active infection will include any patients receiving treatment for infection. Participants with a resolved or chronic HBV infection are eligible if they are:

    - Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG]; or
    - Positive for HBsAg, negative for HBeAg but for >6 months have had transaminases levels below ULN and HBV deoxyribonucleic acid (DNA) levels below 2000 IU/mL (i.e., are in an inactive carrier state).

    Refer to Section 5.3.3 for further details. Screening for chronic conditions is not required.

9. 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.

Prior/concomitant therapy

10. Prior treatment with any chemotherapy, radiation therapy, immunotherapy or investigational agents for NSCLC outside of that received in the definitive setting for Stage III disease (chemotherapy and radiotherapy in SCRT and CCRT regimens is allowed for treatment of Stage III disease). Prior surgical resection (i.e., Stage I, II or III) is permitted.

11. Prior treatment with EGFR-TKI therapy.

12. Major surgery as defined by the investigator within 4 weeks of the first dose of study drug.

13. Patients currently receiving (unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of cytochrome P (CYP)3A4 (at least 3 weeks prior to receiving the first dose of study drug). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.

Prior/concurrent clinical study experience

14. Participation in another clinical study with an investigational product administered in the 4 weeks prior to randomization. Patients in the follow-up period of an interventional study are permitted.

Other exclusions

15. Patient with involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

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

17. Patient was previously randomized in the present study.

18. For female patients only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

19. Contraindication to MRI, including but not limited to, claustrophobia, pace makers, metal implants, intracranial surgical clips and metal foreign bodies.

20. History of hypersensitive to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.

In addition, the following are considered criteria for exclusion from the exploratory genetic research:

1. Prior allogeneic bone marrow transplant.

2. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5.3 Lifestyle restrictions

The following restrictions apply while the patient is receiving study drug (osimertinib or matching placebo) and for the specified times before and after:

5.3.1 Pregnancy

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 a highly effective contraceptive measure from the time of Part II screening until 6 weeks after discontinuing study drug. Acceptable methods of highly effective contraception are provided in Appendix J.

Male patients must use barrier contraceptives (condoms) during sex with a female partner of child-bearing potential (including a pregnant partner) from the start of dosing until 4 months after discontinuing study drug. In addition patients should refrain from donating

sperm from the start of dosing until 4 months after discontinuing study drug.

5.3.2 Blood donation

Patients are prohibited from donating blood from the date of randomization until 28 days after the last dose of study treatment.

5.3.3 Chronic HBV infection

In patients with chronic HBV infection (inactive carrier state) on treatment with osimertinib:

- where ALT exceeds 2 x ULN and 2 x baseline, measurement of HBV DNA as per local practice and/or hepatologist consultation is recommended.

- if biochemical or clinical signs of liver disease or viral reactivation occur, careful monitoring is required.

5.4 Meals and dietary restrictions

Osimertinib can be taken without regard to food. However, patients should avoid taking dietary supplements or herbal medicines with known strong inducers of CYP3A4 whenever feasible (see Section 6.5.1).

5.5 Screen failures

Screen failures are defined as patients who signed the ICF of part I and/or part II to participate in the clinical study but are not subsequently entered to Part II screening or randomly assigned to study treatment in the study. 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 SAE).

Individuals who do not meet the criteria of screening for participation in this study (screen failure) may be rescreened, with the exception of patients in Part I screening with a central EGFR test negative for Ex19del or L858R. Rescreened patients should use the same patient number assigned previously at the first time of screening via IVRS/IWRS. However rescreening should be documented so that its effect on study results, if any, can be assessed.

These patients should have the reason for study withdrawal recorded in the source documents and electronic case report form (eCRF).

5.6 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug. There can be no exceptions to this rule. Where a patient does not meet all the eligibility criteria but is randomized 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 Study Physician must ensure all decisions are appropriately documented. The investigator should make documentation in medical record as appropriate.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (IP; including placebo) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to osimertinib and matching placebo.

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply osimertinib and matching placebo. See Table 4 further details on the IPs.

Table 4 Study treatments

	Osimertinib	Placebo
Study treatment name:	Osimertinib (AZD9291)	Placebo
Dosage formulation:	80 mg tablet for oral administration	80 mg placebo tablet matching osimertinib in size, color, weight, and appearance for oral administration
Dosage formulation, dose reduction:	40mg tablet for oral administration	40mg placebo tablet matching osimertinib in size, color, weight, and appearance for oral administration
Route of administration	Oral	Oral
Dosing instructions:	One tablet of 80 mg per day	One tablet of 80 mg placebo per day
Dosing instructions, dose reduction	One tablet of 40 mg per day	One tablet of 40 mg placebo per day
Packaging and labelling	Osimertinib will be provided in in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Osimertinib matching placebo will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca

Patients should swallow one tablet QD. Tablet can be taken whole with approximately 240 mL water, with or without regard to food.

Study drug will be distributed as following:

- Randomization to week 24 – enough study drug for 4 weeks.
- Week 24 to week 48 – enough study drug for 8 weeks
- Week 48 onwards – enough study drug for 12 weeks

Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Study drug will only be dispensed to patient at randomization day (visit 2) after all study procedures and assessments have been performed as described in Table 1 and all eligibility criteria have been met.

Randomization will be made in IVRS/IWRS system as soon as all the eligibility criteria are met as confirmed by the investigator. It should be documented in the medical records in a proper manner.

Every effort should be made to minimize the time between randomization and starting study treatment. It is recommended that patients commence study treatment as soon as possible after randomization and whenever possible within one day. (i.e., on the same day after randomization in the IVRS/IWRS)

The initial dose of osimertinib/placebo 80 mg QD can be reduced to 40 mg QD to allow for management of IP-related toxicities (see Section 6.6 and Section 8.4.4). Once the dose of osimertinib/placebo is reduced to 40 mg QD, the patient will remain with the reduced dose until termination from study treatment. Re-challenge of 80 mg/placebo is not allowed in this study.

On site visit days on which PK samples are scheduled, the dosing should be delayed until arrival at the site. Patients should not take their dose until instructed to do so by site personnel.

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

The reason for a 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.

Open-label osimertinib will be supplied by AstraZeneca. See Section 7.6 for further details of drug supply following the final OS analysis.

Additional information about osimertinib may be found in the Investigator's Brochure.

6.2 Preparation/handling/storage/accountability

6.2.1 Preparation and Handling

No additional preparation and handling is required for osimertinib or placebo.

6.2.2 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottles specifies instruction of appropriate storage.

6.2.3 Accountability

The investigator or delegated site staff 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.

Only patients enrolled in the study may receive study treatment and only authorized 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 investigator, institution, or the head of the medical institution (where applicable) is accountable for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction should be signed.

Used/unused study drug will be disposed of at site and not returned to AstraZeneca for disposal. Disposal will be performed as per local procedures.

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 study drug from receipt by the study site until the return of all unused study drug 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 study drug.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Methods For Randomization

Patients must not be randomized unless all eligibility criteria have been met.

All patients will be centrally assigned to randomized study treatment in a 2:1 ratio osimertinib: placebo respectively using an IVRS/IWRS.

Randomization will be performed within 6 weeks of completion of chemoradiation. All patients will be stratified at randomization based on prior chemoradiation strategy (CCRT

vs SCRT), tumor stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs. enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity).

Before the study is initiated, the telephone number and call-in directions 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 the IVRS/IWRS assigned patient number cannot be reused.

The IVRS/IWRS will provide to the Investigator(s) or pharmacists the bottles identification number to be allocated to the patient at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

6.3.2 Methods For Blinding

Study drug will be labelled using a unique material pack code, which is linked to the randomization code. The IVRS/IWRS will assign the bottles of study material to be dispensed to each patient. This is a double-blind study wherein each patient will receive either the active osimertinib or osimertinib-matching placebo. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the medication.

6.3.3 Blind Break

The IVRS/IWRS will be programmed with blind-breaking instructions. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. Additionally, patients with BICR- confirmed progression of disease may be unblinded.

AstraZeneca 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. In this case, AstraZeneca 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 and eCRF as applicable. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally- related to an investigational product and that potentially require expedited reporting to regulatory authorities.

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.

The personnel analyzing the pharmacokinetic samples will be unblinded to the investigational treatment for each patient.

6.4 Treatment compliance

The administration of all study drugs including placebo should be recorded in the source

document and appropriate sections of the eCRF. Any change and the reasons for changing the dosing schedule, dose interruption, dose reduction, dose discontinuation, overdosing or omission will also be recorded in the source document and eCRF. This information plus drug accountability for all study drugs at every visit will be used to assess compliance with the treatment.

The study drugs should be completely reconciled with supportive evidence provided in the source document such as drug accountability log or equivalent documents.

The delegated site staff is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) or designee(s) is responsible for ensuring that the patient has returned all unused IP.

Osimertinib/matching placebo 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 patient at each visit and take appropriate steps to optimize compliance.

6.5 Concomitant therapy

Any concomitant treatment, procedures, medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving within 4 weeks prior to the first dose of study drug or receives during the study until 28-day follow-up visit (28 days after last dose of study drug) must be recorded in the source document and the applicable section of eCRF. If any concomitant therapy is administered due to new or unresolved AE, it should be recorded until the related AE is resolved, stabilized, is otherwise explained or patient is lost to follow-up.

6.5.1 Restricted and prohibited concomitant medications

Restricted and prohibited concomitant medications are described below:

- Once enrolled, all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known strong inducers of CYP3A4 whenever feasible; but patients may receive any medication that is considered essential for patient management. Such drugs must have been discontinued for an appropriate period before the first dose of study treatment and for a period of 2 weeks after the last dose of osimertinib or matching placebo. All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring, and on washout periods is provided (See Appendix I).

- If medically feasible, patients taking regular medication, with the exception of strong inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon Breast Cancer Resistance Protein (BCRP) and/or P-glycoprotein (P-gp) with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a

result of increased exposure of the concomitant medication whilst receiving osimertinib. (See Appendix I).

- 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.

- Other anti-cancer therapies, investigational agents, and radiotherapy should not be given while the patient is on study drug.

- Pre-medication will be allowed after, but not before, the first dose of study drug. This includes management of diarrhea, nausea, and vomiting, which should be administered as directed by the Investigator.

6.5.1.1 Drugs known to prolong QTc interval

Current information on drugs known to prolong QTc interval can be found on the Arizona Center for Education and Research on Therapeutics website https://www.crediblemeds.org/.

The website categorizes drugs based on the risk of inducing TdP. During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website. Drugs that prolong the QT interval and are clearly associated with a **known risk of TdP**, even when taken as recommended must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Appendix I. These drugs should not be co-administered with study treatment (osimertinib/placebo) and for a period of two weeks after discontinuing study treatment.

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 with ECGs and electrolytes is recommended.

Patients with congenital long QT syndrome (CLQTS) are excluded from this study.

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

6.5.2 Other concomitant treatment

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 source document and appropriate sections of eCRF.

6.6 Dose modification

Dose modifications are permitted for the management of adverse reactions, as described in Table 5. Further information is provided in Section 8.4.4.

Table 5 Study treatment dose adjustment information for adverse reactions

Target Organ	Adverse Reactions [a]	Dose Modification
Pulmonary	Pneumonitis [b]	Refer to pneumonitis guidelines provided in Table 10 in Section 8.4.4.2.
Cardiac	Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute) at 2 separate ECGs.	Withhold TAGRISSO until QTc interval is < 481 msec or recovery to baseline if baseline QTc is ≥ 481 msec within 3 weeks of interruption, then restart at a reduced dose (40 mg) 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). If the toxicity does not resolve to ≤grade 1 within 3 weeks of interruption the patient will be permanently withdrawn from study treatment.
	QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia	Permanently discontinue study treatment
Cutaneous	Stevens Johnson Syndrome; Toxic epidermal necrolysis	Permanently discontinue study treatment
Blood and lymphatic system	Aplastic anemia	Permanently discontinue study treatment
Other	Grade 3 or higher adverse reaction	Withhold study treatment up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding study treatment for up to 3 weeks	Study treatment may be restarted at the same dose (80 mg/placebo) or the lower dose (40 mg/placebo)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue study treatment

a. The intensity of the clinical AEs graded by the National Cancer Institute (NCI) CTCAE version 5.0
b. Including pneumonitis/ILD and radiation pneumonitis

6.7 Treatment after the end of the study

After the final OS analysis, the study blind will be broken at the site and patient level.

AstraZeneca will continue to supply osimertinib in the continued access phase of this study and after completion of this study while, in the opinion of the Investigator, the patient is benefiting.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patient(s) currently receiving treatment with osimertinib may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patient who would be eligible to move to such a study would be given a new informed consent, as applicable.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from IP in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study. Patients will continue in follow-up per the protocol.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Patients experiencing any of the following AEs will be discontinued from study treatment:
  - Grade 3 or higher pneumonitis
  - Grade 2 pneumonitis where symptoms have not resolved and treatment has not been restarted within 4 weeks after interrupting study treatment
  - Recurrent symptomatic pneumonitis following prior dose interruption and study treatment re-challenge
  - QTc interval prolongation with signs/symptoms of serious arrhythmia
  - Grade 3 or higher adverse reaction that does not improve to Grade 0-2 and treatment has not been restarted within 3 weeks of interrupting study treatment
  - Any AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Severe non-compliance with the Clinical Study Protocol (CSP) as judged by the Investigator and/or AstraZeneca representative
- Pregnancy

- Initiation of alternative anticancer therapy including another investigational agent
- Prior to primary PFS analysis: Objective disease progression as per RECIST v1.1 assessed by BICR
- Post-primary PFS analysis: Disease progression as assessed by investigator
- Patients who are incorrectly initiated on study treatment.

See the SoA (Table 1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

At any time, patients are free to discontinue study treatment or withdraw from the study without prejudice to further treatment. The investigator or delegated site staff should instruct the patient to contact the site before or at the time if study treatment is permanently stopped. A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the source document and eCRF. All study treatment should be returned by the patient at their 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.

Discontinuation of study treatment, for any reason, does not impact on the patient´s participation in the study. The patients should continue attending subsequent study visits and data collection should continue according to the study protocol. 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 including new AEs and follow up on any ongoing AEs and concomitant medications. This could be a telephone contact with the patient at 28 days (+ 7 days) after study treatment is discontinued, 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.

The discontinuation visit should be performed as soon as patient permanently discontinues from study treatment and/or study. See SoA (Table 1) for study of assessments to be performed at treatment discontinuation visit. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

7.1.1.1 Progression follow-up

7.1.1.1.1 Prior to primary PFS analysis

Prior to the primary PFS analysis patients who discontinue study drug for reasons other than RECIST v1.1 defined progression as assessed by BICR will continue RECIST v1.1 assessments every 8 weeks for the first 48 weeks and every 12 weeks afterwards (relative to date of randomization) until RECIST v1.1 defined progression as assessed by BICR

occurs.

In addition to tumor assessments, the following assessments are also required during the follow-up period (as detailed in the SoA [Table 1]):

- WHO Performance Status
- Plasma samples for circulating tumor DNA (ctDNA) and blood borne biomarkers
- Anti-cancer and surgical treatments
- HRU Module
- SAEs and AESIs considered related to study treatment and study procedures
- Electronic Patient Reported Outcomes (ePROs) to be carried out at the same frequency as treatment period:
  - European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire- Lung Cancer 13 items (QLQ-LC13)
  - EORTC Quality of Life Questionnaire – Core 30 items (QLQ-C30)
  - Patients Global Impression of Severity (PGIS)
  - PRO-CTCAE
  - EuroQoL 5-Deimension 5-Levels (EQ-5D-5L)

7.1.1.1.2 Post primary PFS analysis

After the primary PFS analysis, patients who are in progression follow-up will have progression assessed in accordance with local clinical practice. Formal RECIST v 1.1 measurements will not be collected.

ePROs, HRU, WHO performance status, ctDNA and blood borne biomarkers will no longer be required. The patients should return the ePRO devices to site at their next visit and site staff should perform the “End LogPad Use”, so that this is recorded in the database. Only AESIs and SAEs considered related to prior study treatment will be captured.

Patients will enter survival follow-up as described in Section 7.1.1.2. Visits will occur every 12 weeks relative to their last progression follow up visit prior to the primary analysis data cut-off date.

7.1.1.2 Survival follow-up

Survival follow-up is applicable for:

- Patients who have had BICR confirmed RECIST v1.1 defined progression prior to the

primary PFS analysis

- Patients who have withdrawn consent and have agreed to be followed up for survival
- Patients remaining in progression follow-up after the primary PFS analysis (as described in Section 7.1.1.1.2)

7.1.1.2.1 Prior to primary PFS analysis

Patients will be followed up for survival status every 12 weeks until death, withdrawal of consent or the end of the study i.e., at the time of final OS analysis, whichever occurs first. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. In addition to the survival status, the following assessments are also required:

- Anti-cancer and surgical treatments
- Subsequent response/progression until the first disease progression as assessed by the investigator occurs on a subsequent treatment.
- HRU Module
- SAEs and AESIs, if considered related to prior study treatment or open-label osimertinib
- ePROs to be completed at RECIST v1.1 defined progression as assessed by BICR, and week 8, 16 and 32 post-progression, relative to the treatment discontinuation visit:
  - EORTC QLQ-LC13
  - EORTC QLQ-C30
  - PGIS
  - PRO-CTCAE
  - EQ-5D-5L

Patients should be contacted in the week following the data cut-off at the time of primary PFS analysis to provide complete survival data.

For patients who have not actively withdrawn consent, the status of those ongoing, withdrawn (from the study), and "lost to follow-up" at the time of the first OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

7.1.1.2.2 Post primary PFS analysis

Patients will be followed up for survival status every 12 weeks until death, withdrawal of consent or the end of the study i.e., at the time of final OS analysis. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. In addition to the survival status, the following assessments are also required:

- Anti-cancer and surgical treatments
- SAEs and AESIs, if considered related to open-label osimertinib

Patients should be contacted in the week following the data cut-off for the final OS analysis to provide complete survival data.

For patients who have not actively withdrawn consent, the status of those ongoing, withdrawn (from the study), and "lost to follow-up" at the time of the final OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

7.2 Treatment with open-label osimertinib

Treatment assignment may be unblinded for each patient with BICR-confirmed progression per RECIST v1.1 if progression occurs prior to the primary PFS analysis, or based on investigator-assessed progression after the primary PFS analysis. Patients may receive open-label osimertinib if:

- Progression is confirmed by BICR, or, if progression occurs after the primary PFS analysis, investigator-assessed progression has been diagnosed.
- In the opinion of the treating physician, they are continuing to derive clinical benefit (for patients assigned to the osimertinib treatment arm), or, treatment is in accordance with local clinical practice and the judgement of their treating physician (for patients assigned to the placebo arm).
- They have not received any other anti-cancer therapy following the discontinuation of study treatment. Palliative radiotherapy is allowed.
- Disease extent has been characterized by CT or MRI scan at the time of progression.

All patients receiving open-label osimertinib post-progression will enter survival follow-up as described in Section 7.1.1.2. During treatment with open-label osimertinib, the investigator should monitor the patient per local clinical guidance.

Treatment with open-label osimertinib may continue until the patient stops deriving

clinical benefit (as judged by the investigator).

7.3 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

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 e.g. 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.

7.4 Withdrawal from the study

A patient may withdraw from the study (e.g. 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 (e.g. telephone contact, a contact with a relative or treating physician, or information from medical records).

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/or analysis including optional testing, and the investigator must document this in the site study records. The AstraZeneca study team should be informed of withdrawn patient sample destruction by the site or at the central laboratory in a prompt manner.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up patients until 28 days after discontinuation of study treatment or beyond as medically indicated. The patient or the representative will return all unused study treatment and ePRO devices.

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 until the final OS analysis from publicly available sources, in accordance with local regulations. Knowledge of the vital status in all patients is crucial for the integrity of the study.

See SoA (Table 1), for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.5 Patient management post primary PFS analysis and up to final OS analysis

The primary analysis of PFS will occur when approximately 120 progression events confirmed by BICR have been observed out of the globally randomized patients. Following the primary PFS analysis, patients still on study treatment should continue to receive study treatment. Study assessments will continue as per the SoA (see Table 1). Disease status will be monitored as per standard local practice and formal RECIST measurements will not be collected. Patients can continue to receive study treatment until disease progression occurs as judged by the investigator, or until meeting any other discontinuation criteria defined in Section 7.1. Patients with investigator-assessed disease progression may be unblinded and offered open-label osimertinib consistent with the guidance in Section 7.2.

For all patients receiving open-label osimertinib, treatment with open-label osimertinib should continue until radiological or clinical disease progression or unacceptable toxicity as determined by the investigator, at which point open-label osimertinib may be discontinued. Treatment with open-label osimertinib may continue post-progression if the treating physician considers the patient to still be deriving clinical benefit.

AstraZeneca will collect information (during the treatment period and for 28 [+ 7] days after last dose) on SAEs and AESIs related to study treatment, overdose and pregnancy (as per Section 8.4) via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES). Drug accountability information will be recorded in the source documents.

7.6 Patient management post-final OS analysis

The final analysis of OS will be conducted at approximately 60% data maturity, when approximately 120 death events (across both arms) have occurred. At this time point, the clinical study database will close to new data.

Patients will be monitored in accordance with the investigator’s standard clinical practice or national product label. Dispensing of osimertinib post-final OS analysis will be done outside of IVRS/IWRS. At routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed at the site.

AstraZeneca will collect information (during the treatment period and for 28 [+ 7] days after last dose) on SAEs, AESIs, overdose and pregnancy (as per Section 8.4) via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES). Drug

accountability information will be recorded in the source documents.

If an investigator learns of any SAEs or AESIs, including death, at any time after a patient has discontinued study treatment (plus 28-day follow-up), and he/she considers there is a reasonable possibility that the event is causally related to osimertinib, the investigator should notify AstraZeneca (see Section 8.4). Additionally, as stated in Section 8.3.3, any SAE or non-serious AE that is ongoing at the time of this data cut off, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

For details regarding study treatment after the final OS analysis, see Section 6.7.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timings are summarized in the SoA (Table 1). The investigator will ensure that data are recorded in the eCRF. The RAVE Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator ensures the accuracy, completeness, of the eCRF including: 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 eCRF. A copy of the completed eCRF will be archived at the study site at study end.

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), are essential and required for study conduct.

All evaluations in Part I and Part II screening must be completed and reviewed to confirm that potential patients meet all eligibility criteria. 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.

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

8.1 Efficacy assessments

8.1.1 Screening tumor sample for EGFR mutation analysis

8.1.1.1 Biopsied tissue samples for EGFR mutation testing

8.1.1.1.1 Patients *without* a positive local tissue-based EGFR mutation test result

Mandatory provision of a FFPE tumor tissue sample is required for prospective central

analysis of EGFR mutation status in Part I screening. The sample will also be used for exploratory biomarker analysis (except in China as per local regulations).

Cytology samples including fine-needle aspirates (FNA), transbronchial needle aspirates (TBNA), bronchial washings, bronchial lavage, bone marrow aspirates and expectorated sputum are **NOT** acceptable samples and should not be sent. Needle biopsies in which the tissue architecture is maintained are acceptable.

The Investigator will be asked to provide:

- Formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks, not older than 12 months or

- Preferably at least 12 re-cut unstained sections from FFPE tumor tissue block (except in China) (see the Laboratory Manual for the minimum number of slides required), presented on slides and not older than 60 days. Each section is to be 5 μm thick.

Note: Blocks should be provided wherever possible.*

* Note: China study sites will not submit tumor tissue blocks, and only unstained sections from the tissue block will be submitted for further analysis. Mutation testing residual tissue samples collected in China will be destroyed or repatriated maximally 5 years after study indication approval for marketing in China.

If the first tissue sample submitted for central testing is not confirmed as EGFR mutation positive due to test failure, a further tissue sample may be submitted for central testing. Central retests on a new tissue sample can only be performed if the original testing failed. Re-tests are not permitted if the central EGFR tissue testing result is EGFR mutation negative for Ex19del and/or L858R.

Whilst eligible EGFR mutations for this study are Ex19del and L858R, other EGFR mutations (including T790M) will be reported as part of the cobas® EGFR Mutation Test v2.

8.1.1.1.2 Patients *with* a positive local tissue-based EGFR mutation test result

Investigators should provide a FFPE tumor tissue sample (where available) for retrospective central analysis of EGFR mutation status in Part II screening. The sample will also be used for exploratory biomarker analysis (except in China as per local regulations).

If patients have results from a local tumor tissue **cobas®** EGFR Mutation Test v2 test conducted in a central Covance laboratory following its instructions for use for other AstraZeneca studies, retrospective central analysis of EGFR mutation status will not be needed.

Whilst eligible EGFR mutations for this study are Ex19del and L858R, other EGFR mutations (including T790M) will be reported as part of the local EGFR test. Similarly

Ex19del, L858R and other EGFR mutations (including T790M) will be reported from the central retrospective testing of sample if provided.

The local EGFR test results should be collected and maintained as source document and captured in the eCRF entirely by the site.

Tissue sample requirements are as per Section 8.1.1.1.1*.

* Note: China study sites will not submit tumor tissue blocks, and only unstained sections from the tissue block will be submitted for further analysis. Mutation testing residual tissue samples collected in China will be destroyed or repatriated maximally 5 years after study indication approval for marketing in China.

8.1.1.2 Plasma samples for EGFR mutation testing

Mandatory provision of 20 ml of blood is required for retrospective EGFR mutation testing from patients at Part II screening. Blood should be processed to plasma and frozen as soon as possible (within 4 hours), sites should then ship directly to the testing lab. For China, the volume of blood required is 10 ml*.

Further guidance is provided in the laboratory manual.

* Note: Mutation testing residual plasma samples collected in China will be destroyed or repatriated maximally 5 years after study indication approval for marketing in China.

8.1.2 RECIST v1.1

All subjects should continue to receive randomized study treatment until objective radiological disease progression per RECIST v1.1 and as assessed by BICR, or until another discontinuation criterion is met as per Section 7.1.

Tumor assessments will be performed using (i) contrast enhanced CT of the chest and abdomen (including liver and adrenal glands) as the preferred method. However, if subjects are contraindicated to CT contrast agents a non-contrast CT otherwise MRI will be acceptable; and (ii) Contrast enhanced T1w MRI of the brain as the preferred method. However in those subjects who are contraindicated to Gd-DTPA based contrast agents a non-contrast MRI would be sufficient.

CT (preferred) or MRI of chest and abdomen and MRI of the brain will be performed at all tumor imaging visits. The baseline assessment is part of the screening procedures and should be performed ≤28 days prior to randomization. The imaging modality used for baseline tumor assessment, (CT/MRI) for chest and abdomen and MRI for brain, should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible.

Efficacy for all patients will be assessed by objective tumor assessments every 8 weeks (relative to the date of randomization) until 48 weeks, then every 12 weeks thereafter, until confirmed objective radiological disease progression as defined by RECIST v1.1 and as assessed by BICR. These assessments should occur irrespective of whether a patient is

receiving study treatment or has previously discontinued study treatment for another discontinuation criterion and may have started alternative anticancer treatment. Additional scans should be performed if clinically indicated, i.e., if disease progression is suspected. An MRI scan with contrast should be performed in the event of suspected CNS progression. If an unscheduled assessment is performed, and the patient's disease has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

All imaging assessments (including unscheduled visit scans, radiotherapy planning scan, and high resolution CT) will be sent to AstraZeneca appointed central reader on an ongoing basis. Assessment of scans by BICR will be triggered only upon investigator-assessed progression and the results of the BICR will be reported back promptly to sites. If the BICR confirms disease progression study treatment will be discontinued and the patients will enter survival follow up. If the BICR does not confirm disease progression, study treatment should be continued and tumor assessments continued in line with the SoA. Since the primary analysis of the study is based on BICR, it is important that study treatment and scheduled imaging assessments continue until progression confirmed by BICR.

If at the time of primary PFS analysis it is identified that a patient has disease progression by BICR that has not been identified by the investigator, AstraZeneca will contact the investigator to discuss whether continued treatment with study medication is appropriate.

8.1.2.1 Central reading of scans

All imaging scans for tumor assessments including unscheduled visit scans should be duplicated and collected on an ongoing basis and sent to the appointed CRO to enable BICR.

Following BICR-confirmed progression patients should have tumor assessments as per standard local practice for assessment of PFS2 (see Section 8.1.2.2).These local-practice scans should not be sent to the appointed CRO.

The radiotherapy planning scans from the definitive radiation treatment delivered prior to randomization are to be submitted to the AZ appointed imaging CRO to assist in the selection of target lesions (TLs) and in the interpretation of scans during study treatment and to facilitate the interpretation of radiological findings consistent with pneumonitis (radiation vs drug induced pneumonitis).

Information collected in the eCRF regarding prior radiotherapy will also be provided to the BICR to allow the selection of the appropriate TLs.

RECIST v1.1 criteria will be used to assess each patient's tumor response to treatment and allow calculation of PFS, ORR, DoR, DCR, tumor shrinkage and time to death or distant metastases (TTDM). The RECIST v1.1 guidelines for measurable, non-measurable, TLs and non-target lesions (NTLs), and the objective tumor response criteria (CR, PR, SD, or

progression of disease [PD]) are presented in Appendix F).

8.1.2.2 Assessment of second progression

Following objective progression that is confirmed by BICR, patients will have their progression status recorded every 12 weeks per local standard clinical practice to assess PFS2. A patient's progression status is defined according to the local practice and may involve any of: objective radiological progression (preferred), symptomatic progression, or death. Scans will be performed according to the local practice and formal RECIST measurements will not be collected for assessment of PFS2. The second progression event must have occurred during or after treatment with a subsequent treatment after the progression event used for the primary variable PFS or death. The date of PFS2 assessment and Investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the source documents and the eCRF.

Assessment of PFS2 will no longer be collected after the primary PFS analysis.

8.1.3 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. PROs is one of the types of COAs. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of anyone else. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be collected: EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, PRO-CTCAE and EQ-5D-5L (See Appendix G).

PROs will be collected for all patients throughout the study period via a hand-held electronic device. See SoA (Table 1) for the timing of collection. The PRO devices should be administered prior to first dose at visit 2/randomization. Site staff should stress that the information is confidential.

After randomization, ePRO questionnaires are available on electronic devices (LogPads) for a period of up to 7 days for each assessment (i.e., it will be available three days before the designated "Study Day" and three days after the designated "Study Day") for completion. ePRO questionnaires can only be completed once within the 7-day period of availability. ePRO completion is mandatory to those sites that have it approved by health authority/ethic committee/independent review board. In case a patient is not eligible to complete the ePROs e.g., due to sight impairment, illiteracy, sites are required to still assign the LogPad and then immediately perform the "End LogPad Use", so that this is recorded in the database. The relevant actions should be recorded in source document.

For patients who discontinue study treatment prior to BICR-confirmed progression, PROs should be collected at the study treatment discontinuation visit and continue to be collected at the same frequency as the treatment period during progression follow-up until BICR-confirmed disease progression, then at the disease progression visit and at week 8, week 16 and week 32, relative to the disease progression visit.

For patients who have had BICR-confirmed RECIST v1.1 defined progression prior to the primary PFS analysis, ePROs should be completed at week 8, 16 and 32 post-progression, relative to the date of the treatment discontinuation visit. PROs will not be collected for any patient after the primary PFS analysis.

8.1.3.1 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30)

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning (Health Related Quality of Life [HRQoL]) and symptoms (Aaronson et al 1993) for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, nausea, and vomiting); a 2-item global HRQoL scale; 5-single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, diarrhea) 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.

8.1.3.2 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13)

The EORTC QLQ-LC13 is a well-validated complementary module measuring lung cancer associated symptoms and side effects from conventional chemotherapy and radiotherapy (Bergman et al 1994). Refer to Appendix G. The EORTC QLQ-LC13 includes questions assessing cough, hemoptysis, dyspnea, site specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy, and alopecia (treatment-related side effects) and pain medication.

8.1.3.3 Patients Global Impression of Severity (PGIS)

The PGIS item is included to assess how a patient perceives his/her overall current severity of cancer symptoms. Patients will choose from response options from "no symptoms" to "very severe."

8.1.3.4 Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Event (PRO-CTCAE)

The PRO-CTCAE system was developed by the National Cancer Institute (NCI) in recognition that collecting potential treatment-related symptoms directly from patients can improve the accuracy and efficiency. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Sprangers & Aaronson 1992; Litwin et al 1988; Basch et al 2009). The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The PRO-CTCAE is an item-bank of symptoms experienced by patients while undergoing treatment of their cancer. To date, 81 symptoms of the CTCAE have been identified to be amenable to patient reporting but not all items are administered in any one clinical trial. Response options vary from frequency, severity, and interference with usual activities. For this study, 14 items are considered relevant for this cancer treatment (See Appendix G).

8.1.3.5 EuroQoL 5-Dimension 5-Levels (EQ-5D-5L)

The EuroQoL 5-Dimension (EQ-5D) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions as follows: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options ("no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems") that reflect increasing levels of difficulty (EuroQol Group 2015).

Since 2009, the EuroQol Group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L) that expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Janssen et al 2008a, Janssen et al 2008b, Pickard et al 2007).

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analog scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (see Appendix G).

8.1.3.6 Administration of electronic Patient Reported Outcomes

The order of ePRO completion via hand-held electronic device will be as following: EORTC QLQ-LC13, EORTC QLQ-C30, PGIS, PRO-CTCAE and EQ-5D-5L.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- Site staff to explain that it is important to hear directly from the patients how they feel. Investigator or delegated site staff should also stress that the information is confidential. Therefore, if the patient has any medical problems he/she should discuss them with the investigator or site staff separately from the ePRO assessment.

- Remind patients that there are no right or wrong answers; avoid bias by not clarifying items.

- Train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor. Also provide guidance on whom to call if there are problems with the device by providing the patient information pamphlet provided by the ePRO vendor.

- The investigator or delegated site staff should review the compliance of ePRO

completion with subjects at each study visit. Any compliance issue should be discussed with subjects and is encouraged to work on a solution to enhance/resolve the issue. Certain discussion and compliance review should be reflected in source document.

- Electronic devices (LogPads) used for ePRO collection should be return to site at the nearest visit as soon as the last assessment is completed by patient.

Monitor compliance: minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

8.1.4 Health Resource Use Module

HRU Module will be completed by the investigational site for any healthcare resource use between visits. Up to the point of primary PFS analysis, the site will ask patients for any HRU between visits (i.e., excluding routine follow-up clinic visits associated with the clinical trial but including both planned and unplanned admissions) at study visits as per Table 1.

Patients who discontinue study treatment for a reason other than BICR-confirmed progression should have information collected at that time of study treatment discontinuation, 28-day follow-up and every 8 weeks up to week 48 and then every 12 weeks (relative to the date of randomization) afterwards until BICR-confirmed progression.

Following BICR-confirmed progression, information will be collected every 12 weeks during survival follow-up. Assessments for Healthcare resource will no longer be collected after the primary PFS analysis.

For the purposes of economic evaluation, it is necessary to capture healthcare resource use related to the treatment and the underlying disease. Within the study, the following resource use will be captured:

- Hospital episodes including the type of contact (hospitalizations, outpatient, day case), reason, length of stay (including intensive care unit), and concomitant medications and procedures.

- Symptoms for admission.

The above resource use data will mainly come from the source document including but not limited to medical record and patient interview. The delegated site staff will record it in the Hospital Admissions Details module in the eCRF.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

See Table 6 for the list of clinical safety laboratory tests to be performed for clinical chemistry, hematology and urinalysis and refer to the SoA (Table 1) for the timing and frequency. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA (Table 1). If clinical chemistry, hematology, and urinalysis assessments have been performed within 7 days prior to commencing study treatment, they do not have to be repeated on Visit 2 (Day 1/Week 1) if the patient's condition has not changed (i.e., no new treatment during this period of time, no new complication, or aggravation).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities in documentation. The laboratory results should be signed and dated and retained at center as source data for laboratory variables and applicable section of eCRF in a promptly manner.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

The clinical chemistry, hematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The numbers of samples and blood volumes is therefore subject to site-specific change.

Table 6 Laboratory safety variables

Hematology/Hemostasias (whole blood)	Clinical Chemistry (serum or plasma)
B-Hemoglobin (Hb)	S/P-Albumin
B-Red Blood Cell (RBC) count	S/P-Alanine aminotransferase (ALT)
B-Hematocrit	S/P-Aspartate aminotransferase (AST)
B-Reticulocytes	S/P-Alkaline phosphatase (ALP)
B-Leukocyte count	S/P-Bilirubin, total (TBL)
B-Absolute leukocyte differential count [b]:	S/P-Calcium, total
Neutrophils	S/P-Creatinine
Lymphocytes	S/P-Glucose
Monocytes	S/P-Lactate dehydrogenase (LDH)[a]
Basophils	S/P-Magnesium
Eosinophils	S/P-Potassium
B-Platelet count	S/P-Sodium
Urinalysis (dipstick) [c]	S/P-Urea/Blood Urea Nitrogen
U-Glucose	
U-Protein	
U-Blood	

NB. In case a patient shows an AST **or** ALT ≥3xULN together with TBL ≥2xULN please refer to Appendix E for further instructions.

a LDH is an additional variable collected at Part II screening visit only.

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

c Note: Either dipstick and local lab testing are acceptable methods of urinalysis. The results are to be reported as qualitative outcomes to be comparable to the dipstick results.

8.2.2 Volume of blood

Total mandatory blood volume in the first 12 weeks (up to Visit 6) is approximately 300 mL including optional pharmacogenetics (PGx) sample (see Table 7).

Table 7 Approximate blood sample volumes (mL) [d]

Visit	Safety [a]	PK analysis	Plasma [b]	PGx [c]
Part I Screening	NA	NA	NA	NA
Visit 1/Part II Screening	15	NA	50	6 (Optional)
Subsequent treatment Visit, Visit 2, 3 and 5	15	NA	30	NA
Visit 4 and 6	15	2	30	NA
Subtotal at Visit 6	**90**	**4**	**200**	**6**

NA= not applicable; PGx=pharmacogenetics; PK=pharmacokinetics.

a For safety, assumes 6 mL clinical chemistry and 9 mL hematology per visit. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The blood volume might be

higher at some sites who collects serum samples for pregnancy test. The number of samples/blood volumes is therefore subject to site-specific change.

b Plasma samples collected for retrospective central EGFR mutation testing and Plasma sample for ctDNA and blood borne biomarkers

c Pharmacogenetic testing should occur during Part II screening (subject to consent). However if for any reason the sample is not drawn prior to dosing, it may be taken at any visit after visit 2 until the last study visit.

d The approximate blood sample volume summarized in the table above might not be applicable for China.

Additionally, at Part II Screening, a pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be collected from all women of child-bearing potential only.

8.2.3 Physical examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen and additional systems as deemed clinically appropriate (e.g., skin).

Height will only be measured during the Part II screening, and it will be documented in the eCRF. Weight will be documented in the eCRF. Physical examination and weight will be performed at timelines as specified in the SoA (Table 1).

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 or disease progression, see Sections 8.3.9 and 8.3.10.

8.2.4 Vital signs

Vital signs (to be taken before blood collection for laboratory tests) will be measured in a supine position (or sitting, if supine is not feasible) after 10 minutes rest for the patient in a quiet setting and will include systolic and diastolic blood pressure, and pulse rate.

Any clinically significant changes in vital signs (pulse and blood pressure) should be recorded as an AE if applicable.

8.2.5 Electrocardiograms

Twelve-lead ECG will be performed at the visits indicated in the SoA (Table 1) and in addition should be performed in the event of any cardiac AE.

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at approximately 5 minute 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. A paper copy should be filed in the patient's medical records as source document. If an abnormal ECG finding

at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

ECG data will be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. The investigator may choose to perform a non-digital ECG at the time of the screening visit in order to identify patients eligible for study entry. If a non-digital ECG is performed at the screening visit it cannot subsequently be used as a baseline recording, in this situation an ECG will need to be collected on the baseline visit in digital form. If no digital ECG is captured prior to the start of study treatment, where an appropriate non-digital ECG is available, the non-digital ECG will be used as a baseline recording.

Heart rate, PR, R-R, QRS, QT intervals and QT corrected by Fridericia's formula (QTcF) will be determined and reviewed by an external cardiologist. ECG data used for patient eligibility will be reviewed and determined based on investigator or delegated cardiologist's judgement.

Fridericia's formula is applied to calculate the corrected QT interval.

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

If there is a clinically significant abnormal ECG finding during the Treatment period, this should be recorded in the source document and the AE section of eCRF, according to standard AEs collection and reporting processes. A 28-day follow-up assessment will be required if an on treatment assessment showed a clinically significant abnormality at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

After the primary PFS analysis, there is a potential to move from centrally reviewed to locally reviewed ECGs depending upon the analysis of cardiac data. AstraZeneca will notify sites if local ECG assessment is to be instituted, at which point, ECG assessments will be performed locally (triplicate 12-lead ECG, with paper printouts of 10 seconds for Investigator review) and a paper copy will be stored in the patient's medical records. ECG information will continue to be recorded in the eCRF. If there is a clinically significant abnormal ECG findings during this period, this should be recorded on the AE eCRF, according to standard AEs collection and reporting processes. After final OS analysis, ECG assessments will be performed according to routine clinical practice as defined by the Investigator.

8.2.6 Echocardiogram/MUGA scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits as shown in SoA (Table 1). The modality of the cardiac function assessments must be consistent within a patient i.e., if ECHO is used for the screening assessment then ECHO should also be used

for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken.

ECHO/MUGA assessment at week 36 should be carried out additionally to align the assessment frequency every 12 weeks relative to the date of randomization.

8.2.7 WHO performance status

Performance status will be assessed at the scheduled visits indicated in the SoA (Table 1) according to WHO criteria as follows:

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

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

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

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

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

8.3 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.

AE 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, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the Investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

The AESIs for the study are:

- Pneumonitis
- Interstitial lung disease

- Radiation pneumonitis

Guidelines for dose modifications and management of pneumonitis (including radiation pneumonitis) are provided in Section 8.4.4.2 (See Table 10) of this protocol.

8.3.1 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.

8.3.2 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the time of signature of the Screening Part II ICF throughout the treatment period and including the 28-day follow-up (28 days after last dose of study drug), as shown in Table 8. In addition, any AEs related to study procedures occurring during Screening Part I will be collected. Any new or unresolved AE observed at 28-day follow-up should be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

SAEs will be recorded during the course of the study from the time of signing the first ICF. AESIs will be recorded from the time of signing the Screening Part II ICF. The time period for AE and SAE collection is described in Table 8.

Table 8 Time period and collection of AEs and SAEs

Part I Screening until Part II Screening	Part II Screening until 28-day follow-up visit	Progression follow-up	Survival follow-up	Post final OS analysis for patients on osimertinib
All SAEs, and AEs related to study procedures	All AEs, SAEs, and AESIs	SAEs and AESIs, if related to study treatment **AND** SAEs related to study procedures	SAEs and AESIs, if related to prior study treatment or open-label osimertinib [a]	All SAEs [b]

a Additional safety assessments may be performed as per local clinical practice, but will not be collected as part of study data capture.

b AstraZeneca will collect information (during the treatment period of osimertinib and for 28 [+ 7] days after last dose of osimertinib) on SAEs, overdose and pregnancy (as per Section 8.4) via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES).

All SAEs 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.

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 in accordance with the SAE reporting timelines where relevant.

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.

For those patients who are continuing to receive osimertinib after the final OS analysis, AstraZeneca will collect information (during the treatment period and for 28 (+ 7) days after last dose) on SAEs, overdose and pregnancy (as per Section 8.4) via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES). Drug accountability information will be recorded in the source documents.

8.3.3 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. All SAE/non-serious AEs/AEs of special interest (as defined in Section 8.3), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs/AESIs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but with further recording in the CRF for AESIs only. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused patient's withdrawal from study treatment
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of SAE

8.3.5 Causality collection

The Investigator will assess causal relationship between IP 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 IP?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. 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 to the CSP.

8.3.6 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 had any health problems since the previous visit ?'*, or revealed by observation will be collected and recorded in the Clinical Report Form (CRF). 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 will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs (pulse and blood pressure) should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product, or are considered to be clinically relevant as judged by the investigator.

If deterioration in a laboratory value, vital sign, ECG, ECHO/MUGA, or WHO performance is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory value/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia vs low hemoglobin value). 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 8.3.9 and 8.3.10.

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with TBL ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

8.3.9 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of locally advanced unresectable 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.

8.3.10 Disease progression

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

Progression of the malignancy under study, including signs and symptoms progression, should not be reported as a SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as SAE.

8.3.11 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 cancers are those that are NOT the primary reason for the administration of the study drug and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.12 Handling of deaths

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

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF

module (in the Statement of Death Page), but should not be reported as a SAE during the study.

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

- Deaths with an unknown cause should always be reported as a SAE, but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., 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 one calendar day i.e., 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 RAVE WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the RAVE WBDC system is not available, then the Investigator or other delegated study site staff reports a SAE to the appropriate AstraZeneca representative through alternative reporting way in writing as instructed.

The AstraZeneca representative will advise the Investigator/study site staff how to

proceed.

The reference document for definition of expectedness/listedness is Section 3 (Emerging Safety Information) of the Investigator's Brochure for the AstraZeneca drug, osimertinib

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

If the pregnancy is discovered before the study patient has received any study drug

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

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 abnormalities/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 abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs from the date of first dose of study treatment until 6 weeks after the last dose of study treatment, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within one day i.e., 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 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.2.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), 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 AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

The local study team should adopt the master pregnant partner form in line with local procedures/requirements and submit it to the relevant Regulatory Authority /Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) prior to use.

8.4.3 Overdose

In the context of a clinical study, an overdose is any dose which exceeds the daily dose of 80 mg or 40 mg for patients that have dose reduced, that is defined in the CSP.

A maximum tolerated dose has not been established for osimertinib.

There is no known antidote. Investigators are advised that any patient, who receives a higher dose than intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, no matter it is AEs associated or not, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately via eCRF, 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 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Management of IP-related toxicities

8.4.4.1 General dose adjustments for adverse events

There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If a patient experiences a CTCAE grade 3 or higher toxicity and/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 to osimertinib/matching placebo, dosing of osimertinib/matching placebo will be interrupted and supportive therapy administered as required in accordance with local

practice/guidelines. If a toxicity resolves or reverts to <CTCAE grade 2 within 3 weeks of interruption, treatment with osimertinib / matching placebo may be restarted at the same dose (osimertinib 80 mg / matching placebo) or a lower dose (osimertinib 40 mg / matching placebo), using the rules below for dose modifications (see Table 9), and with discussion and agreement with the AstraZeneca Study Team Physician as needed. If restarting at the same dose level, patients should be closely monitored for 3 days following the restart of treatment. If within 3 days there is recurrence of same toxicity, a dose reduction should be considered at the Investigator's discretion.

Table 9 Dose reduction levels

	Study Treatment
Starting Dose	80 mg osimertinib/ matching placebo
Reduced Dose	40 mg osimertinib/ matching placebo

If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study drug and observed until resolution of the toxicity.

If an AE subsequently requires dose interruption, study treatment may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

Permanent discontinuation due to toxicity

If patients experience any of the following, they will not be permitted to restart study treatment:

- Grade 3 or higher pneumonitis
- Grade 2 pneumonitis where symptoms have not resolved within 4 weeks after interrupting study treatment
- Recurrent symptomatic pneumonitis following prior dose interruption and study treatment re-challenge
- QTc interval prolongation with signs/symptoms of serious arrhythmia
- Any AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing

8.4.4.2 Pneumonitis

Whilst recognizing that radiographic changes coinciding with radiation portals would favor the diagnosis of radiation pneumonitis, differentiating a potential drug-induced pneumonitis from radiation pneumonitis can be challenging. The diagnosis of both events can be very subjective and is typically dependent on physician's judgement based on their clinical experiences and the use of EGFR TKI therapies. Moreover given that the time to onset of such events and their treatment is likely to be similar, a single guidance on dosing

modification and toxicity management for ‘pneumonitis’ is provided in Table 10 which covers both pneumonitis / ILD and radiation pneumonitis, rather than having two separate guidance.

If new or worsening pulmonary symptoms (e.g., dyspnea, cough) or radiological abnormality suggestive of pneumonitis is observed, guidance on investigations and toxicity management, as described in detail in Table 10 will be applied. It is recommended to perform a full diagnostic work-up, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. The results of diagnostic work-up (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. The investigator will be asked to consider whether the signs /symptoms/radiological findings are consistent with radiation pneumonitis, drug-induced pneumonitis/ILD, or other diagnosis.

Table 10 'Pneumonitis'[a] Dosing modification and Toxicity Management Guideline

Grade of the Event (NCI CTCAE version 5.0)	Dose modification	Toxicity management
Any Grade	-	• Monitor patients for signs and symptoms of pneumonitis (new onset or worsening shortness of breath or cough). Patients 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.	**No dose modification required however** • Holding study drug may be considered as clinically appropriate and during diagnostic work-up for other etiologies.	For Grade 1 (radiographic changes only) • Perform investigations as clinically appropriate • Monitor the patient and closely follow-up in 2 to 4 days for clinical symptoms +/- additional assessments and continue to monitor closely thereafter; • Additional imaging on continued treatment may be considered

Table 10 'Pneumonitis'[a] Dosing modification and Toxicity Management Guideline

Grade of the Event (NCI CTCAE version 5.0)	Dose modification	Toxicity management
Grade 2 Symptomatic, medical intervention indicated [b], limiting instrumental ADL.	**Hold study drug until resolution of symptoms** [c] The decision to re-initiate study drug will be based upon treating physician's clinical judgement and following endorsement from the AstraZeneca study physician. • If clinically appropriate to re-initiate, it is recommended that corticosteroids are administered concomitantly and subsequently tapered/withdrawn as clinically appropriate. • Re-initiation at either 80mg/placebo once daily or at a reduced dose of 40 mg once daily/placebo can be considered, as clinically appropriate, and in agreement with the AstraZeneca study physician • If ≥Grade 2 pneumonitis (symptomatic) occurs following re-initiation of study drug, permanently discontinue study drug.	For Grade 2 (mild to moderate new symptoms) • Treat in accordance with local clinical practice. • Following study drug re-initiation, monitor and closely follow-up in 2 to 4 days for recurrence of symptoms and at frequent intervals thereafter • Additional imaging may be considered following re-initiation of study drug
Grade 3 or 4 **Grade 3** Severe symptoms, limiting self-care ADL; oxygen indicated [d] **Grade 4** Life-threatening respiratory compromise, urgent intervention indicated, e.g., tracheostomy or intubation.	**Permanently discontinue study drug**	Severe or new symptoms, new/worsening hypoxia, life threatening Treat in accordance with local clinical practice.

ADL=Activities of daily living

a Includes pneumonitis/ILD and radiation pneumonitis

b Patients given treatment for asymptomatic changes are not mandated to interrupt trial therapy and guidance for Grade 1 should be followed

c Study treatment should be permanently discontinued if symptoms have not resolved within 4 weeks after interrupting study treatment

d Patients given oxygen in the absence of symptoms do not require permanent discontinuation of study drug

8.4.4.3 QTc prolongation

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

Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute) at 2 separate readings should have study drug interrupted and regular monitoring of ECGs performed until resolution to <481 msec, or recovery to baseline if baseline QTcF is ≥481 msec. If the toxicity resolves or reverts to ≤CTCAE grade 1 within 3 weeks of interruption, study drug may be restarted at the same dose or reduced dose using the dose reduction levels in Table 9 with discussion and agreement with the AstraZeneca Study Team Physician as needed. If the toxicity does not resolve to ≤CTCAE grade 1 within 3 weeks of interruption, the patient will be permanently withdrawn from study drug. Study treatment must be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category** as noted in the current guidance in the ArizonaCert website https://www.crediblemeds.org/, close monitoring with ECGs and electrolytes is recommended.

Close monitoring with ECGs and electrolytes is also recommended in patients with congestive heart failure, and/or electrolyte abnormalities.**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.

8.4.4.5 Changes in cardiac contractility

Patients who develop relevant cardiac signs and symptoms should be managed as clinically appropriate, in line with the general toxicity management (Section 8.4.4.1).

8.4.4.6 Erythema multiforme, and 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 study 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 study treatment should be considered. If signs and symptoms suggestive of SJS appear, study treatment should be interrupted. Osimertinib should be discontinued immediately if SJS or

TEN is diagnosed.

8.4.4.7 Aplastic anaemia

Rare reports of aplastic anemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. If signs and symptoms suggestive of aplastic anemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anemia.

8.4.5 Medication error, drug abuse, and drug misuse

8.4.5.1 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 calendar** day i.e., 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 medication error (see Section 8.3.2) and **within 30 days** for all other events.

8.4.5.2 Medication error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP/study intervention or AstraZeneca NIMP that either causes harm to the patient or has the potential to cause harm to the patient.

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

8.4.5.3 Drug abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP 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.

8.4.5.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized 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.

8.5 Pharmacokinetics

Plasma samples of approximately 2 mL will be collected for measurement of plasma concentrations of osimertinib as specified in the SoA (Table 1) at pre-dose on day 29 (visit 4/week 4), day 85 (visit 6/week 12) and day 169 (visit 9/week 24). Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, and align 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 will be recorded.

Samples will be used to evaluate the PK of osimertinib. Pre-dose PK samples should be collected within 1 hour before the dose on the day of collection. The sample collection time and date should be recorded in source document and central lab form. The collection of the plasma sample for PK can be omitted if the patient did not have exposure to IP for at least 7 days prior to the visit.

Drug concentration information that may 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 analyzed in the bioanalytical lab (Covance labs, Harrogate, UK or its affiliate) using 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.

8.5.1 Determination of drug concentration

Samples for determination of osimertinib (and AZ5104) concentrations in plasma will analyzed by Covance on behalf of AstraZeneca. Full details of the analytical method used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (i.e., osimertinib and AZ5104) at the time of receipt by the bioanalytical laboratory will be analyzed.

In addition, the PK samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional drug metabolites and 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, if warranted.

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

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

8.5.2 Storage and destruction of pharmacokinetic samples

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

PK samples may be disposed of or anonymized by pooling. Any results from such analyses may be reported separately from the CSR, if warranted.

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 may be reported separately in a bioanalytical report.

All PK samples and PK testing residual samples collected in China will be managed according to local laws and regulations, and will be destroyed maximally 12 months after the final CSR release.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

Approximately 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. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in 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 genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

Blood samples for genetic analyses will be obtained during the study, except in China as per local regulations.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are

important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.8 Biomarkers & Exploratory Research

Mandatory collection of blood samples and analysis of residual tumor from samples provided for EGFR mutation testing, for biomarker research is also part of this study*. Samples will be collected as specified in the SoA (Table 1).

In addition, an optional fresh tumor biopsy sample at the time of disease progression may be collected from patients.

Tumor and blood samples will be collected and will be tested for exploratory biomarkers to evaluate their association with observed clinical responses to study treatment, including time to progression (the primary endpoint of the study) and ORR.

Further details of exploratory biomarkers are provided in Section 8.8.1.

* Blood and tissue samples for biomarker & exploratory research will be obtained during the study, except in China and other selected countries and study sites, as per local regulations. Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

8.8.1 Exploratory biomarkers

Tumor markers

Based on availability of tissue, tumor material at baseline after central testing of EGFR mutation status (see Section 8.1.1) will be used to assess exploratory biomarkers. Baseline measures will be correlated with outcomes including time to progression and ORR. Markers tested may include but will not be limited to EGFR mutations (sensitizing and non-sensitizing), Human Epidermal Growth Factor Receptor-2 (HER2), and Tyrosine-protein kinase Met (MET) mutations, expression, and amplification.

Tumor material from an optional fresh biopsy at the time of disease progression will be used to understand resistance mechanisms to study treatment. Markers tested may include but will not be limited to the identification of alterations in genes known or potentially involved in EGFR signaling. Tissue requirements for this sample are provided in Section 8.1.1.

Soluble markers

A series of blood samples to generate plasma samples will be collected from all patients. These samples will be used for the extraction and analysis of ctDNA and will be used to explore the relationship between emergence of EGFR sensitizing mutations in ctDNA and time to progression. In addition, resistance mechanisms will be explored. Markers tested may include but will not be limited to T790M, C797S, EGFR amplification, MET amplification, HER2 amplification, and alterations in other genes involved in EGFR signaling. Similarly the relationship between blood-borne biomarkers and drug response and/or disease progression will be explored. These markers may include but will not be limited to growth factors or cytokines.

8.8.2 Additional research

Residual tumor and plasma samples from that provided for mandatory research may be used to explore factors that may influence susceptibility to/development of NSCLC/cancer or and/or response to osimertinib (where response is defined broadly to include efficacy, tolerability or safety). In addition the samples may be used to support the development of diagnostics. This additional research is optional and is subject to additional patient consent.

8.8.3 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

Mutation testing residual plasma and tissue samples collected in China will be destroyed or repatriated maximally 5 years after study indication approval for marketing in China.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The formal statistical analyses will be performed to test the main hypothesis:

- H_0: No difference between osimertinib and placebo.
- H_1: Difference between osimertinib and placebo.

The primary objective of this study is to assess the efficacy of osimertinib compared with placebo in terms of PFS as assessed by BICR. Key secondary endpoints are CNS PFS by BICR and OS.

In order to strongly control the type I error at 5% 2-sided significance level, a sequential testing procedure will be implemented and after the testing of PFS, OS, and CNS PFS will be tested (in that order). The hypothesis on OS will only be tested if the null hypothesis is rejected for PFS. The hypothesis on CNS PFS will only be tested if the null hypothesis is rejected for OS, either at the time of the PFS analysis or at the time of the final OS analysis.

9.2 Sample size determination

Approximately 200 patients in a 2:1 ratio (osimertinib to placebo) will be randomized into the study. Patients will be stratified at randomization based on prior chemoradiation strategy (CCRT vs SCRT), tumor stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity).

The primary endpoint for this study is PFS by BICR in the FAS population. The primary analysis will occur when approximately 120 PFS BICR events have been observed. With 120 PFS (BICR) events the study has 90% power to show a statistically significant difference in PFS at the 2-sided 5% level if the assumed true treatment effect is a HR 0.53; this translates to an approximate 7 month improvement from a median 8 month PFS on placebo. The smallest treatment difference that would be statistically significant is a PFS HR of 0.68 (translating to an approximate 4 month improvement).

In order to provide strong control of the type I error rate, α=0.05 (two-sided), the primary endpoint of PFS (BICR in FAS), OS (FAS), and CNS PFS (FAS) will be tested in this sequential order. If any previous analysis in the sequence is not statistically significant, the alpha will not be transferred to subsequent analyses.

The analyses of PFS, CNS PFS and OS endpoints will occur at the time of the primary analysis of PFS. One analysis of the primary endpoint (PFS by BICR) is planned. Two analyses of OS are planned; one interim at the time of PFS and a final analysis. The final OS analysis is planned to be conducted when the OS data are approximately 60% mature (approximately 120 deaths). The secondary endpoint of OS will be tested at both the interim and final analysis. The alpha level allocated to OS will be controlled at the interim and final timepoints by using the Lan-DeMets spending function for OS that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends upon the proportion of information available.

Approximately 200 patients will be randomized. Of those, it is planned that approximately 30 to 40 patients will be recruited in China. This is being done to ensure adequate Chinese patient participation to satisfy China Regulatory Authority requirements. The China cohort will support standalone safety and efficacy analyses of patients from China.

9.3 Populations for analyses

9.3.1 Full Analysis Set

The FAS will include all randomized patients (see Section 9.6). The FAS will be used for all efficacy analyses and treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received. This is also known as the Intent to Treat (ITT) analysis set.

9.3.2 Safety Analysis Set

The safety analysis set (SAF) will consist of all randomized patients who received at least one dose of study treatment (see Section 9.6). Safety data will not be formally analyzed but summarized using the SAF, according to the treatment received; i.e., erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

9.3.3 Pharmacokinetic Analysis Set

PK Analysis Set is defined as patients in the SAF who have at least one measurable PK concentration, 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 7 continuous days of osimertinib dosing prior to the sample day as well as the sample day. For any individual sample to be included in the PK analysis set, the full sample data and dosing data need to be present for that sample.

The Pharmacokineticist will agree to the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed. Important protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but not limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median time to reach maximum concentration (t_{max}); sample processing errors that lead to inaccurate bioanalytical results; incomplete dose administered; incomplete PK profile collected; and/or use of disallowed concomitant medication. In the case of an important protocol deviation or event, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Important deviations will be listed and summarized in the CSR.

9.3.4 Evaluable for Response Analysis Set

The evaluable for response analysis set will be all patients in the FAS who have measurable disease at baseline according to the BICR of baseline imaging data.

The primary analysis of PFS, and other RECIST-based outcomes by independent central review in the FAS population will be repeated using the evaluable for response analysis set as

sensitivity analyses.

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject 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.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the FAS population. Results of all statistical analyses will be presented using a 95% CI and 2-sided p-value.

9.4.1.1 Analysis of the primary variable

9.4.1.1.1 Primary analysis of PFS

PFS (per RECIST 1.1 as assessed by BICR) is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression. PFS per BICR for patients in the FAS will be analyzed using a log rank test stratified by chemoradiation strategy (CCRT vs SCRT), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC), and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be obtained directly from the U and V statistics as follows (Berry et al 1991; Robins et al 1991; Robins 1993; Selke and Siegmund 1983):

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

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

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

If the resulting number of events per stratum is too small, the strata will be collapsed. Further details are provided in the SAP. A KM plot and summaries of PFS 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) vs log (time) and, if necessary, a time dependent covariate will be fitted to assess the extent to which this represents random variation.

9.4.1.1.2 Sensitivity analyses

(a) **Quantitative Interactions**

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved, then it will be concluded that overall, the treatment effect is consistent across the subgroups. If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process, all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

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

(b) **Ascertainment bias**

The possibility of bias in assessment and measurement of PFS by BICR will be assessed using the Investigator assessment of disease progression by RECIST. The HR from BICR assessment and Investigator assessment of PFS will be assessed. Further details will be provided in the SAP.

(c) **Evaluation-time bias**

In order to assess possible evaluation-time bias that could occur if scans are not performed at the protocol-scheduled time points, the midpoint between the time of progression and the previous evaluable RECIST assessment will be analyzed using a log rank test stratified

chemoradiation (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity), as described for the primary analysis of PFS.

(d) **Attrition bias**

Possible attrition bias will be assessed by repeating the primary PFS analysis, except that the actual PFS event times rather than the censored times of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments, will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. A KM plot of the time to censoring, where the censoring indicator of the primary PFS analysis is reversed, will be presented.

9.4.1.1.3 Subgroup analyses

In addition to the analysis of PFS described above, the following subgroup analyses will be conducted by comparing PFS between treatments (i.e., using a Cox-Proportional Hazards Model) in the following groups:

- Chemoradiation (concurrent vs sequential)
- Disease stage prior to chemoradiation (IIIA vs IIIB/IIIC)
- Patients enrolled at a Chinese site and declaring themselves of Chinese ethnicity vs patients enrolled at non-Chinese site or patients declaring themselves of non-Chinese ethnicity
- Central plasma ctDNA EGFR (Ex19del and L858R) mutation status at screening (positive vs negative vs unknown)
- Tissue EGFR mutation at screening (Ex19del vs L858R)
- Race (Asian vs Non-Asian)

The results of these analyses will be presented in terms of a HR together with its associated 95% CI separately for each subgroup in the comparison. Further details will be outlined in the SAP.

9.4.1.2 Analysis of secondary variables

9.4.1.2.1 Hierarchical testing of key secondary variables

The secondary endpoints of OS and CNS PFS in the overall population will be tested after the

primary PFS analysis in a hierarchical procedure at the time of the PFS analysis, following the primary analysis (see Section 9.1).

9.4.1.2.2 Analysis of overall survival

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

The analysis of OS will be conducted at 2 time points: At the time of the primary analysis of PFS; and At approximately 60% maturity (when approximately 120 death events across both arms have occurred). OS data will be analyzed using the same methodology and model as for the analysis of PFS provided there are sufficient events (≥ 20 deaths across both treatment groups with at least 5 events per arm) available for a meaningful analysis otherwise descriptive summaries will be provided.

9.4.1.2.3 Analysis of Objective Response Rate

ORR is defined as the percentage of patients with at least one BICR-assessed visit response of CR or PR. ORR by BICR will be analyzed using a logistic regression stratified by chemoradiation (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity). The results of the analysis will be presented in terms of an OR together with its associated 95% profile likelihood CI and 2-sided p-value.

9.4.1.2.4 Analysis of Duration of Response

DoR will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The expected DoR (EDoR) is the product of the proportion of patients responding to treatment and the mean DoR in responding patients, and provides an estimate based on all randomized patients. Treatments will be compared by calculating the ratio of EDoRs using an appropriate probability distribution for DoR in responding patients. The choice of probability distribution will be detailed in the SAP. The analysis of DoR will be stratified by the same stratifiers as the primary analysis, weighting each stratum inversely proportional to the within stratum variance of the log of the ratio of EDoRs. Additionally, descriptive data will be provided for the DoR in responding patients, including associated KM curves (without any formal comparison or p-value attached).

9.4.1.2.5 Analysis of Disease Control Rate

DCR is defined as the percentage of subjects who have a best overall response of CR or PR or SD.

DCR, by BICR, will be analyzed using a logistic regression. The results of the analysis will be presented in terms of an OR together with its associated 95% profile likelihood CI and 2-sided p-value.

DCR [DCR: CR + PR + SD] and OS.

9.4.1.2.6 Analysis of tumor shrinkage

Depth of response (i.e., tumor shrinkage / change in tumor size) by BICR will be examined by summarizing the absolute change in TL tumor size from baseline, and percentage change in TL tumor size from baseline using descriptive statistics and presented at each time point and by randomized treatment group. The effect of osimertinib on best percentage change in tumor size will be estimated from an analysis of covariance (ANCOVA) model. The number of patients, unadjusted mean, and least squares means for each treatment group will be presented, together with the difference in least squares means, 95% CI and corresponding p-value.

9.4.1.2.7 Analysis of time to death or distant metastases

Distant metastases free survival, by BICR, for patients in the FAS will be analyzed using a log rank test stratified by chemoradiation (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be obtained as for progression free survival.

TTDM will be defined as the time from the date of randomization until the first date of distant metastasis or date of death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1 or proven by biopsy. Patients who have not developed distant metastasis or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment.

However, if the patient has distant metastasis or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 (date of randomization) unless they die within 2 visits of baseline.

9.4.1.2.8 Analysis of time to CNS PFS

Time to CNS PFS, is the time to the earlier event of CNS progression or death using BICR assessments, according to RECIST v1.1. Patients in the FAS will be analyzed using a log rank test stratified by chemoradiation (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient

declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be obtained as for progression free survival.

Cumulative incidence of brain metastases, by BICR, will be summarized using appropriate summary statistics, and further details will be provided in the SAP. Cumulative incidence rate of CNS PFS by BICR at 12 and 24 months will be presented.

9.4.1.2.9 Time to study treatment discontinuation

Time to study treatment discontinuation or death (TTD), for patients in the FAS will be analyzed using a log rank test stratified by chemoradiation (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be obtained as for progression free survival.

TTD is defined as the time from randomization to the earlier of the date of study treatment discontinuation (regardless of the reason for study treatment discontinuation) or death (i.e. date of study treatment discontinuation/death or censoring – date of randomization + 1). Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive. Patients who have not been treated will be censored at the date of randomization.

9.4.1.2.10 Analysis of post progression outcomes

PFS2, time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST) patients in the FAS will be analyzed using a log rank test stratified by chemoradiation (concurrent vs. sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China Cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be obtained as for progression free survival.

For details of PFS2 refer to section 8.1.2.2. Analysis of PFS2 will only take place at the time of the primary PFS analysis. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression; i.e., censored at the last progression assessment date if the patient has not had a second progression or death.

TFST or death is defined as the time from the date of randomization to the earlier of start date

of the first subsequent anti-cancer therapy following discontinuation of randomized treatment, or death. Any patient not known to have had a subsequent therapy or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy; i.e., the last follow-up visit where this was confirmed.

TSST or death is defined as the time from the date of randomization to the earlier of the start date of the second subsequent anti-cancer therapy following discontinuation of randomized treatment, or death. Any patient not known to have died at the time of the analysis and not known to have had a second subsequent therapy will be censored at the last known time to have not received second subsequent therapy, i.e., the last follow-up visit where this was confirmed.

9.4.1.2.11 Analysis of EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall QoL will be assessed using EORTC QLQ-C30 and QLQ-LC13 (secondary endpoints). 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, and will only take place at the time of the primary PFS analysis. 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 (dyspnea, insomnia, appetite loss, constipation, and diarrhea), 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, hemoptysis, dyspnea, 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 dyspnea, all are single items. The dyspnea scale will only be used 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/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. 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 minimized.

Definition of compliance and evaluability rates

Compliance rates for the PRO questionnaires should be at least 85%; this rate will be monitored as the trial goes on. Compliance with the EORTC QLQ-C30 and EORTC QLQ-LC13 will be calculated, separately for each questionnaire:

$$\text{Compliance rate} = \frac{\text{number of evaluable forms}}{\text{number of expected forms}} \times 100$$

Evaluability rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 will also be calculated, separately for each questionnaire:

$$\text{Evaluability rate} = \frac{\text{number of evaluable forms}}{\text{number of received forms}} \times 100$$

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

An evaluable form = a questionnaire with a completion date and at least one subscale that is non-missing.

A received form = a questionnaire that has been received and has a completion date and at least one individual item completed.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically relevant change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-C30 and the QLQ-LC13 (Osoba et al 1998). For example, a clinically relevant deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline (defined as Day 1, pre-dose) of ≥10. A clinically relevant improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsening as shown in Table 11. Patients with no baseline data will be excluded from analyses.

Table 11 Visit responses for symptoms and HRQoL

Score Change from baseline Visit response	Score Change from baseline Visit response	Score Change from baseline Visit response
QLQ-C30/QLQ-LC13 symptom scales/items	≥+10 ≤-10 Otherwise	Worsened Improved Stable
QLQ-C30 functional scales and global health status/QoL	≥+10 ≤-10 Otherwise	Improved Worsened Stable

HRQoL=Health-related quality of life; QLQ C30 30-Item core quality-of-life questionnaire; QLQ-LC13 13-Item lung cancer quality-of-life questionnaire.

Time to symptom and HRQoL/function deterioration (QLQ-C30 and QLQ-LC13)

Time to deterioration in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

Improvement in symptom and HRQoL (QLQ-C30 and QLQ-LC13)

Improvement in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

9.4.1.2.12 Safety

Safety data will be summarized using appropriate summary statistics and further details will be provided in the SAP. The safety endpoints are:

- AEs (graded by CTCAE v5, including AESIs);
- Clinical chemistry, hematology and urinalysis;
- Vital signs (pulse and blood pressure), physical examination, weight;
- ECG parameters;
- LVEF by ECHO/MUGA scan;
- WHO Performance Status.

9.4.1.2.13 Pharmacokinetics

PK data from this study will be analyzed using a population PK approach and may also form part of a pooled analysis with other osimertinib studies; results from these analyses may also be reported separately from the CSR. Pharmacokinetic concentration data will be summarized using appropriate summary statistics, and further details will be provided in the SAP.

9.4.1.3 Exploratory analysis

9.4.1.3.1 Relationship between PK and other variables

Correlation of PK with other primary, secondary or exploratory endpoints in patients treated with osimertinib. Results from such analyses may be reported separately from the CSR, if warranted.

Data from this study may also form part of a pooled analysis with other osimertinib studies.

9.4.1.3.2 Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event System

PRO version of the CTCAE data will be presented using summaries and descriptive statistics and further details will be provided in the SAP.

9.4.1.3.3 Patients Global Impression of Severity

PGIS data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

9.4.1.3.4 EQ-5D-5L health state utility index

EQ-5D-5L health state utility index data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

9.4.1.3.5 Healthcare Resource Use Module

HRU data will be presented using summaries and descriptive statistics, based on the FAS and further details will be provided in the SAP.

9.4.1.3.6 Comparison of baseline tumor EGFR mutation status

Baseline tumor EGFR mutation status will be compared between tumor DNA and plasma ctDNA using the Kappa coefficient. Analysis will be carried out separately for each sensitizing mutation, Ex19del and L858R. Analysis will be in all Part II screened patients with evaluable results from baseline plasma samples.

Baseline tumor EGFR mutation status will also be compared between local and central (**cobas**® EGFR mutation test v2) tests, using the Kappa coefficient, in subjects with evaluable results from baseline tumor samples. Analysis will be carried out separately for each sensitizing mutation, Ex19del and L858R, and as well as in aggregate.

9.4.2 Methods for multiplicity control

The multiple testing procedure will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint of PFS and key secondary endpoints, OS and CNS PFS. The family-wise error rate is strongly controlled at

5% (two sided) for these endpoints.

The testing procedure is sequential in that it starts with testing the primary endpoint of PFS. If the PFS analysis is significant at the primary analysis, then 5% alpha will be recycled to the OS endpoint and then CNS PFS endpoint.

To provide strong control of the type I error rate, α=0.05 (two-sided), the primary endpoint of PFS, and endpoints of OS and CNS PFS, will be tested in this sequential order. If any previous analysis in the sequence is not statistically significant, the alpha will not be transferred to subsequent analyses.

The analyses of PFS, OS, and CNS PFS endpoints will occur at the time of the primary analysis of PFS. If the OS analysis is statistically significant at the time of the PFS analysis or the final OS analysis, then the significance testing of CNS PFS will be performed at the full α=0.05 significance level (two-sided). If the OS analysis is not statistically significant at the time of the PFS analysis or the final OS analysis then the significance testing of CNS PFS will be not be performed.

Since two analyses of OS are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the two planned analyses of OS.

The significance level for the OS analyses will be calculated using the statistical software package EAST by specifying the information fraction for each analysis. The information fraction is calculated as the number of OS events at the analysis time-point divided by the total number of events at the final analysis time-point. For example, assuming a median OS on the placebo arm of 40 months and a median OS of 50 months on the osimertinib arm, 48 OS events were observed at the interim analysis, the information fraction would be 0.40 (48/120 events) for the interim analysis and 1.00 for the final analysis. This would result in a significance level for the interim analysis of 0.0008 (2-sided) and a significance level for the final analysis of 0.0497 (2-sided).

The information fraction is calculated as the number of events at the analysis time-point divided by the total number of events at the final analysis time-point.

Any non-statistically significant OS analyses at the time of the primary analysis of PFS will not preclude further testing of OS.

9.5 Interim analyses

The SAP will describe the planned interim analyses in greater detail.

9.5.1 Independent data monitoring committee

An IDMC will be convened, and will meet to review unblinded safety data, initially approximately 6 months after the study has started, as long as a minimum of 20 patients have been randomized and treated for >1 month. 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.

9.6 China Cohort

Approximately 200 patients will be randomized. Of those, it is planned that approximately 30 to 40 patients will be recruited in China. This is being done to ensure adequate Chinese patient participation to satisfy China Regulatory Authority requirements. The China cohort will support standalone safety and efficacy analyses of patients from China.

The China cohort consists of all Chinese patients from Chinese sites accredited by Chinese regulation.

Hence a patient randomized in the China cohort will be included in the China FAS.

The analysis of PFS in the China cohort will be conducted at the same time as the analysis of PFS for the overall population.

The final OS analysis in the China cohort will be conducted at the same time as the final OS analysis for the overall population.

Per China Regulatory Authority guidance, in addition to the evaluation of global cohort data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in China and Asia population is required to facilitate the benefit-risk assessment for Chinese patients. Hence, the safety and efficacy data in China cohort will be analyzed separately where the same endpoint definitions and the same analysis methods (as detailed in Section 9.4) are applied.

The China FAS (China FAS) will include all patients randomized in China sites and claimed themselves as ethnicity Chinese, China FAS will be used for all China only efficacy analyses.

The China SAF is defined as patients in the China FAS and who received at least 1 dose of study treatment and for whom post-dose data are available.

The China Pharmacokinetic Analysis Set is defined as patients in the China FAS who have

at least one evaluable PK concentration.

All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or patients are available, otherwise descriptive statistics only will be presented. No adjustment for multiplicity will be made and so the procedure for hierarchical testing detailed in Section 9.4 will not be followed. PFS efficacy evaluation for China cohort will be performed only once.

Details of China cohort analysis, including vendor to perform the analysis, will be specified in China supplementary SAP, which is to be finalized before global cohort data lock for analysis.

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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 International Council for Harmonisation (ICH) 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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

AstraZeneca will be responsible for obtaining the required authorizations 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, 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 the sponsor of a 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.

- 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

Prompt notification by the investigator to the sponsor 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 subject or the reliability and robustness of the data generated in the clinical trial.

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 he or she becomes aware of it.

In certain regions/countries, the sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- The sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. If EU Clinical Trials Regulation 536/2014 applies, the sponsor is required to enter details of serious breaches into the European Medicines Agency (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 the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor

A 2 Financial disclosure

Investigators and sub-investigators will provide AstraZeneca 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.

Patients must be informed that their participation is voluntary. Patients or their legally authorized 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 center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients 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 patient or the patient's legally authorized 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 patients partner becomes pregnant, 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. Any intention and embarkation of re-screening should be well communicated with AstraZeneca study team and reflected the reason in the medical records. Both the previous signed ICF and re-screened ICF should be retained in original copy at study site.

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 and potential diagnostic development. 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 analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Patients will be assigned a unique identifier by AstraZeneca. Any patient records or data sets transferred to the AstraZeneca will contain the identifier only; 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 AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.

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 AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The patient 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 authorized or does not have a business need to know the information.

The patient must be informed that in some cases their data may be pseudonymized. The General Data Protection Regulation (GDPR) defines pseudonymization 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 organizational 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, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] 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:

[1] The data controller determines the purposes for which and the means by which personal data is processed, as defined by the European Commission

- 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 (e.g., 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.

Notification of personal Data Breach to patients:

- notification to patients 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 patients. The site and/or Principal Investigator shall conduct the notification by contacting the patients 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 patients. If the personal data breach needs to be notified to the patients, the notification to patients 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 patients.

- 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 patients. 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 patients. 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 patients. 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 patients, where applicable

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the CSP and letters to Investigators.

A 6 Dissemination of clinical study data

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 description of this clinical study will be available on http://astrazenecaclinicaltrials.com, http://www.clinicaltrials.gov, and https://euclinicaltrials.eu/ as will the summary of the study results when they are available. The clinical trial and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic 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.

Monitoring details describing strategy, including definition of study-critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan(s).

The sponsor 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.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

AstraZeneca assumes accountability for actions delegated to other individuals (e.g., CROs).

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 the local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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.

A 9 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 AE is the development of any untoward medical occurrence in a patient or clinical study patient (other than progression of the malignancy under evaluation) administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. 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 SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality 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.

B 3 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 (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). 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.

B 5 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 (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity rating scale: CTCAE

The grading scales found in the revised NCI CTCAE latest version 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 7 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 8 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 e.g., medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, e.g., wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. 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 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 authorized product information, or for unauthorized 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 center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

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.

AstraZeneca 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 and will be registered by the AstraZeneca Biobank Team during the entire 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.

Biological samples collected in China will be stored and disposed of according to local laws and regulations.

Mutation testing residual tissue samples collected during Part I and Part II screening in China will be destroyed or repatriated maximally 5 years after study indication approved for marketing in China.

Mutation testing residual plasma samples collected during Part I and Part II screening in China will be destroyed maximally 5 years after study drug indication approved for marketing in China.

All PK samples and PK testing residual samples collected in China will be managed according to local laws and regulations, and will be destroyed maximally 12 months after final CSR release.

C 2 Withdrawal of Informed Consent for donated biological samples

AstraZeneca ensure that biological samples are returned to the source or destroyed at the end of a specified period as described in the information consent.

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 analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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:

- are to be packed and shipped in accordance with IATA Instruction 602.

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, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. 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 - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

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 etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/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 trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA, i.e., the entire genome.

The results of genetic analyses may be reported in the 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 Study treatment continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

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 fulfill all of the inclusion criteria described in the main body of the CSP **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:

- Prior allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

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 CSP.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, 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.

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 last patient 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 sample 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.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix B.

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 center. 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.

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.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyses 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.

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 SAP may be prepared where appropriate.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of HL. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 8.3.8 of the CSP.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

AST or ALT ≥ 3× ULN **together with** TBL ≥ 2×ULN at any point during the study following the start of study treatment irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN

- TBL ≥ 2 × ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4 Safety Reporting)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met.[#]

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix B 5.
- A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (e.g., chronic or progressing malignant disease, severe infection or liver disease), or did the patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix E 6

If **No**: Follow the process described in Appendix E 4.1.

If **Yes**: Determine if there has been a significant[#] change in the patient's condition compared with when PHL criteria were previously met.

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix E 4.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Guidelines for evaluation of objective tumor response using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) for this study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiologic progression.

Definitions of measurable, non-measurable, target and non-target lesions

Patients with measurable disease and/or non-measurable and/or no evidence of disease assessed at baseline by CT/ MRI will be entered in this study.

Measurable:

A lesion, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis[1] diameter of ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Brain metastasis

[1] The short axis is defined as the longest axis perpendicular to long axis
[2] Nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as TL.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location, are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (e.g., adrenal glands) is considered as a single organ. Each segmented organ (e.g., liver) or lobular organ (e.g., lung) is considered as a single organ.

Prior irradiated lesions may be considered measurable and selected as TLs provided they fulfill the other criteria for measurability.

Non-target lesions:

Additional measurable and non-measurable lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

Methods of assessment

The same method of assessment on the same imaging technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in Table 12, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 12 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET

CT Computed tomography; FDG-PET ^{18}F-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible images for measurement of TL, assessment of NTL, and identification of any new lesions.

It is recommended that CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement should be additionally imaged based on the signs and

symptoms of individual patients. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV contrast of the abdomen is appropriate. In patients with severely compromised renal function a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast enhanced CT*. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility and scanner across all imaging timepoints per patient.

* In this study all patients will have MRI of brain at screening, at each RECIST tumor assessment following randomization and if CNS progression is suspected.

Clinical examination

Clinical examination of skin lesions or surface tumors (by visual inspection or manual palpation) will not be used for RECIST assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

X-ray

Chest X-ray

Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

Ultrasound examination will not be used for RECIST assessment of tumors as it is not a reproducible method, does not provide an accurate assessment of tumor size, and it is subjective and operator dependent. Tumors identified by ultrasound examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology

Histology on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (e.g., ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the RECIST 1.1 tumor response assessments in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to new lesions or progression of NTLs, respectively.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in the event that positive hotspots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hotspot on a bone scan that cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that timepoint.

FDG-PET scan

^{18}F-Fluoro-deoxyglucose PET/CT (FDG-PET) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[3] not present on the most recent FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT examination is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

[3] A positive FDG-PET scan lesion should be reported only when an uptake (e.g., SUV) greater than twice that of the surrounding tissue or liver is observed.

Tumor response evaluation

Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient (e.g., new lesions) at follow-up. An MRI scan with contrast should be performed in the event of suspected CNS progression.

Baseline assessments should be performed ≤28 days prior to randomization, and ideally should be performed as close as possible to the start of IP. Efficacy by RECIST 1.1 for all patients will be assessed according to the schedules of assessments. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

For patients who discontinue IP due to toxicity in the absence of evidence of disease progression, tumor assessments should be continued according to the original imaging schedule.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a TL has completely disappeared, the longest diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New lesion.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g., definitive radiotherapy, embolization, surgery etc. during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST CRF for that timepoint and in all subsequent TL assessments (see 'Not evaluable' below). If a TL has been completely removed (surgery) or disappears following an intervention, the longest diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New lesion.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 13).

Table 13 Evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (e.g. missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the PD criteria, PD overrides not evaluable as a TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 14).

Table 14 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

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

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as RECIST 1.1 progression. The finding of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of a radiological response; it is a reason for stopping study therapy.

Patients with symptomatic deterioration requiring discontinuation of treatment without objective radiologic evidence of disease progression at that time should continue to undergo tumor assessments where clinically feasible.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 15.

Table 15 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline).

Central Review

All tumor assessment images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, storage at the Investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. Assessment of scans by BICR will be triggered only upon investigator-assessed progression and the results of the BICR will be reported back typically within two working days to sites.

Further details of the BICR will be documented in the Independent Review Charter (IRC), (also referred to as 'Imaging Charter') and the CNS IRC.

Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

If specified, all images will be collected, quality checked and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data and transfer to the imaging CRO will be provided in a separate document.

Also if specified, further details of the BICR will be documented in the Independent Review Charter (also referred to as the 'Imaging Charter').

CT Scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax, abdomen, and pelvis examination. For brain imaging, MRI with IV contrast is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular

institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies e.g. neck) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

References

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix G Patient Reported Outcome

ENGLISH

EORTC QLQ-C30 (version 3)

Patient Reported Outcomes questionnaires EORTC QLQ-C30 removed due to copyrights.

Patient Reported Outcomes questionnaires EORTC QLQ-C30 removed due to copyrights.

Patient Reported Outcomes questionnaires EORTC QLQ-LC13 removed due to copyrights.

Patient Global Impression of Severity for Cancer Symptoms

Patient Reported Outcomes questionnaires PGIS removed due to copyrights.

NCI PRO-CTCAE™ ITEMS

Patient Reported Outcomes questionnaires PRO-CTCAE removed due to copyrights.

NCI PRO-CTCAE™ ITEMS

Patient Reported Outcomes questionnaires PRO-CTCAE removed due to copyrights.

NCI PRO-CTCAE™ ITEMS

Patient Reported Outcomes questionnaires PRO-CTCAE removed due to copyrights.

Health Questionnaire

English version for Canada

Patient Reported Outcomes questionnaires EQ-5D-5L removed due to copyrights.

Patient Reported Outcomes questionnaires EQ-5D-5L removed due to copyrights.

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADRs	Adverse Drug Reactions
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state [amount·time/volume]
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
CCRT	Concurrent Chemoradiation
CDx	Companion diagnostic
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CLQTS	Congenital Long QT Syndrome
$CL_{ss/F}$	Apparent total body clearance at steady state
CNS	Central Nervous System
COA	Clinical Outcome Assessment
COCs	Combined Oral Contraceptives
CONSORT	CONsolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CRT	ChemoRadioTherapy
CSP	Clinical Study Protocol
CSR	Clinical Study Report

Abbreviation or special term	Explanation
C_{ss}, max	Maximum plasma concentration at steady state
C_{ss}, min	Minimum plasma concentration at steady state
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumor DeoxyriboNucleic Acid
CYP	Cytochrome P
DCR	Disease Control Rate
DTPA	Diethylenetriamine penta-acetic acid
DILI	Drug Induced Liver Injury
DNA	DeoxyriboNucleic Acid
DoR	Duration of Response
DUS	Disease-Under Study
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EGFRm	EGFR mutation
EGFRwt	eEGFR wild type
EM	Erythema Multiforme
EOD	Every Other Day
EORTC QLQ LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
ePRO	electronic Patient Reported Outcome
EQ-5D-5L	EuroQoL 5-Dimension 5-Levels
ESMO	European Society for Medical Oncology
Ex19del	Exon 19 deletion
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluoro-DeoxyGlucose Positron Emission Tomography
FFPE	Formalin Fixed and Paraffin Embedded

Abbreviation or special term	Explanation
FNA	Fine-Needle Aspirates
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
Gd	Gadolinium
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HBc IgG	hepatitis B core antibody
HDPE	High-Density Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HR	Hazard Ratio
HRCT	High-Resolution Computed Tomography
HRQoL	Health-Related Quality of Life
HRU	Health Resource Use
IASLC	International Association for the Study of Lung Cancer
IATA	International Airline Transportation Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMRT	Intensity-Modulated Radio Therapy
IP/IMP	Investigational Product
IRB	Institutional Review Board
IRC	Independent Review Charter

Abbreviation or special term	Explanation
ITT	Intent To Treat (population)
IUD	Intra-uterine Device
IUS	Intra-uterine System
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
L858R	An amino acid substitution at position 858 in EGFR, from a leucine (L) to a arginine (R)
LDH	Lactate DeHydrogenase
LH	Luteinizing Hormone
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
MET	Tyrosine-protein kinase Met
MMRM	Mixed effect Models for Repeated Measures
MRI	Magnetic Resonance Imaging
MUGA	Multigated Acquisition Scan
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not Evaluable
NIMP	Non-Investigational Medicinal Product
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-Target Lesion
OR	Odds ratio
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed death-1
PD-L1	Programmed Death Ligand 1
PET	Positron Emission Tomography

Abbreviation or special term	Explanation
PFS	Progression-Free Survival
PFS2	Progression-Free Survival-Second (time to second progression on a subsequent treatment)
PGIS	Patients Global Impression of Severity
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PHL	Potential Hy's Law
PK	Pharmacokinetics
PO	Per Os (taken orally)
PR	Partial Response
PRO	Patient Reported Outcomes
PRO-CTCAE	Patient Reported Outcome-Common Terminology Criteria for Adverse Event
PS	Performance Status
QD	Quaque Die (once a day)
QLQ-C30	30-Item Core Quality-of-Life Questionnaire
QLQ-LC13	13-Item Lung Cancer Quality-of-Life Questionnaire
QoL	Quality of Life
QTc	corrected QT
QTcF	QT corrected by Fridericia's formula
RBC	Red Blood Cell
RECIST v 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCRT	Sequential Chemoradiation
SD	Stable Disease
SJS	Stevens Johnson Syndrome
SoA	Schedule of Activities
SoC	Standard of Care
t_{max}	Time – maximum (time to reach maximum concentration)

Abbreviation or special term	Explanation
T790M	An amino acid substitution at position 790 in EGFR, from a threonine (T) to a methionine (M)
TBL	Total Bilirubin
TBNA	TransBronchial Needle Aspirates
TdP	Torsades de Pointes
TEN	Toxic Epidermal Necrolysis
TFST	Time to First Subsequent Therapy
TKI	Tyrosine Kinase Inhibitor
TL	Target Lesion
TNM	Tumor/Node/Metastasis
TSST	Time to Second Subsequent Therapy
TTD	Time to Treatment Discontinuation or death
TTDM	Time to Death or Distant Metastases
UK	United Kingdom
ULN	Upper Limit of Normal
US(A)	United States (of America)
V	Visit
vs	versus
w	Weeks
WBDC	Web Based Data Capture
WBRT	Whole Brain RadioTherapy
WHO	World Health Organization
WoCBP	Women of Childbearing Potential

Appendix I 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 eCRF.

DRUGS INDUCING CYP3A4 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH STUDY TREATMENT

Osimertinib is metabolized by 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.

Table 16 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to Study treatment start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Phenobarbitone	5 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. Please contact AstraZeneca with any queries you have on this issue.

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).

Table 17 Exposure, pharmacological action and toxicity may be increased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin	

Table 17 Exposure, pharmacological action and toxicity may be increased by Osimertinib

Warning of possible interaction	Advice
Sulfasalazine	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with Study treatment.
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	

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 website: https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing TdP.

During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 18 and should not be co-administered with study treatment (osimertinib/placebo) and for a period of two weeks after discontinuing study treatment. 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 website to provide the most up to date information.

Table 18 Drugs with a known risk of TdP

Drug name	Withdrawal period prior to study treatment start
Aclarubicin, 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

Table 18 Drugs with a known risk of TdP

Drug name	Withdrawal period prior to study treatment start
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*, Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

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 with ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome (CLQTS) are excluded** from this study.

Guidance regardless of TdP risk category

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

Appendix J Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

Definition of Women of Childbearing Potential

Women of Childbearing Potential (WoCBP):

Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilized or post-menopausal (definitions below):

Permanent sterilization 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 (e.g. 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 over 50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.

Acceptable 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 (e.g. less than 1 percent per year) when used consistently and correctly.

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)
- Vasectomized 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

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 IUDs
- Fertility awareness methods
- Coitus interruptus

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